TREATMENT OF CENTRAL NEUROPATHIC PAIN CAUSED BY NEUROMYELITIS OPTICA SPECTRUM DISORDER

by

Maureen A. Mealy

A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland

March 2019

Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disease of the central nervous system that preferentially targets the optic nerves and spinal cord, leading to paralysis, blindness and death. Severe pain is a disabling component of the disease with up to 91% of patients reporting pain that is classified as central neuropathic pain (CNP), which is often refractory to treatment commonly used for peripheral neuropathy. This dissertation is comprised of two parallel studies both meant to inform a large Phase III study.

The first part involves a Phase II randomized single blinded, sham-controlled study proposes to evaluate the acceptability, feasibility, safety and efficacy of a novel technique called Scrambler Therapy for CNP treatment in patients with NMOSD. Scrambler is a non-invasive pain modifying technique that utilizes transcutaneous electrical stimulation of nociceptive fibers with the intent of re-organizing maladaptive signaling pathways. It has been examined for treatment of peripheral neuropathy with favorable outcomes, but there exists little data for use in CNP. Twenty-two participants were recruited from the Johns Hopkins NMO Clinic and were eligible for inclusion if they had CNP rated at 4 or higher on an 11-point numeric rating scale (0-10). Participants were randomized 1:1 and blinded to undergo either Scrambler Therapy or sham daily for 10 days. The primary outcome was a significant reduction in pain following 10-day treatment in the Scrambler intervention versus sham arm. The secondary outcome was safety, acceptability and feasibility. Sustainability of effect was also be evaluated. As the first-ever interventional pain study in NMOSD, it sets the foundation for future work that focuses on alleviating the physical and emotional suffering of patients who have neuropathic pain. As the first known study to investigate use of Scrambler

for central neuropathic pain treatment, it further acts as a model for other diseases, including multiple sclerosis, spinal cord injury and stroke.

The second study involves a cross-sectional assessment of pain on co-occurring symptoms in patients with NMOSD, which include anxiety, depression and sleep disturbance, and the impact of pain on quality of life (QoL). This involves a convenience sampling of 72 patients diagnosed with NMOSD who completed each of the following surveys to determine pain, health-related QoL, anxiety, depression and sleep disturbance, respectively: Brief Pain Inventory (BPI), Short Form-36 Health Inventory (SF-36), Neuro-QoL [Quality of Life in Neurological Disorders] Short Form v1.0 – Anxiety, Neuro-QoL Short Form v1.0 – Depression, and Neuro-QoL Short Form v1.0 - Sleep Disturbance. This study broadens the understanding of how intervening on pain can enhance QoL.

Advisors:
Sharon Kozachik, PhD, RN, FAAN
Michael Levy, MD, PhD
Thomas J. Smith, MD
Jerilyn Allen, ScD, RN
Marie Nolan, PhD, RN, FAAN

Funding for this study was made possible through a research grant provided by the Johns Hopkins Blaustein Pain Research Committee.

This research was made possible in part through a training grant provided by the Johns Hopkins Institute for Clinical and Translational Research (ICTR) which is funded in part by Grant Number TL1 TR001078 from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Johns Hopkins ICTR, NCATS or NIH.

I dedicate this dissertation to each of the following:

To my mentor, my boss, my champion and my friend, Michael Levy. You have believed in me and helped me to believe in myself so that I could confidently pursue this PhD, and so much more. I literally would not be the person I am today if anyone other than you were my boss over this past decade. Any success I've had, and any success I will have in the future, is due in no small part to you. It is through your dedication to research in NMOSD that my passion was born.

To my parents. Without you, I could not have gotten through this. Particularly over the last several months since my Ryan Patrick was born, I've leaned on you to pick up the slack and act as primary caregivers as I labored over a computer analyzing and writing… analyzing and writing… and analyzing and writing some more.

To my sister Melanie. Even though you are of this earth in spirit only, you supported me throughout my whole life. I learned perseverance and how to be methodical from you. Love you to the moon and back… I know you continue to dance with the angels!

And finally, to my Remarkable Ryan. Since the moment you were born, anything I do is for you, for us. I waited a long time for your soul to find mine, and boy, was it ever worth the wait! You have brought color to my world. You are my love and my life. You are my everything. I love who you are and I can't wait to find out who you will become!

Acknowledgements:

This dissertation would not have been possible without the advice and mentoring of my dissertation committee: Sharon Kozachik, Jerilyn Allen, Thomas J. Smith, Marie Nolan, and, last but never least, Michael Levy. Their guidance and support have been instrumental to my success throughout this iterative process. I can see the influence of every single committee member on this final product and feel fortunate to have been able to bring together this expert committee.

Thanks to Thomas J. Smith for providing the training in Scrambler therapy, to Giuseppe Marineo and Stephen D'Amato for acting as advisors, DIS&L for supplying the GEOMC Pain Scrambler model MC-5A machine, to Lauren Totonis for being an exceptionally dedicated (and unpaid) study coordinator, to Larry Cook for statistical support, and to my classmates for their constant encouragement.

Thank you to my father, Hugh M. Mealy, for assembling and maintaining the sham device, even at 2 am when it needed repair before the next day's treatments, and for driving my 9-month pregnant self all around the DMV to patients' homes so that I did not have to lug around equipment on my own.

Finally, a special note of thanks to our patients. The grace, resilience and dedication they show every day in the face of adversity is truly inspiring.

Dissertation Organization

This dissertation contains five chapters. The first chapter provides background, theoretical underpinnings, significance, and specific aims. Chapter two (Manuscript 1) is a review of the current state of the science of central neuropathic pain treatment as it relates to quality of life outcomes. It is currently in press with *Pain Management Nursing*. Chapters three and four (Manuscripts 2 & 3) are data-based manuscripts. Chapter three has been submitted to *Neurology* and includes results and analyses from Aims 1 & 2 of the study. Chapter four has been submitted to *Journal of Neurological Sciences* and provides results and analyses from Aim 3. Chapter five summarizes findings and discusses implications for nursing practice and future research.

Table of Contents

Chapter 1: Introduction to and Significance of Central Neuropathic Pain in Neuromyelitis Optica Spectrum Disorder

Persistent pain is a common and often frustrating problem for patients and health care providers, affecting approximately 100 million U.S. adults and costing $500-635 billion annually, according to the Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education (2011). While estimates are varied, central neuropathic pain (CNP) constitutes a large percentage of persistent pain, and is associated with worse health than is non-neuropathic pain (Cohen & Mao, 2014). Neuropathic pain from any etiology is characterized by agonizing burning, shooting or tingling sensation in the face, arms, torso and legs caused by nerve damage (Cohen & Mao, 2014; Dworkin et al., 2007). It is particularly difficult to treat with only 40-60% of people achieving even partial relief (Dworkin et al., 2007). CNP experienced by patients with neuromyelitis optica spectrum disorder (NMOSD) is particularly refractory to available treatments (Qian et al., 2012). NMOSD is a chronic relapsing autoimmune disease of the central nervous system that preferentially targets the optic nerves and spinal cord, leading to blindness, paralysis and death (Wingerchuk, Hogancamp, O'Brien, & Weinshenker, 1999). Pain is more prevalent in NMOSD than in most other neurological diseases with up to 91% of patients reporting CNP (Zhao, Mutch, Elsone, Nurmikko, & Jacob, 2014; Pellkofer et al., 2013; Kanamori et al., 2011; Borsook, 2012). Spinal CNP typically presents weeks to months after the cord damage has occurred, long after the acute injury, and may be the result of secondary changes due to reorganization of damaged circuits of the somatosensory system (Sjolund, 2002). CNP occurs at and below the spinal cord lesion level, and can persist for years, decades or throughout the patient's life. The impact of CNP on quality of life (QoL) is profound. Research in NMOSD

has found that those patients with CNP experience depression, decreased enjoyment of life, and difficulty with ambulation (Zhao et al., 2014; Pellkofer et al., 2013; Mutch, Methley, Moore, & Jacob., 2014). NMOSD is a severely disabling disease and there remains a high unmet need for effective treatment of CNP, thus allowing for an opportunity for investigation.

Epidemiology of Pain in Neuromyelitis Optica Spectrum Disorder

NMOSD is a rare disease disproportionately affecting non-Caucasians and females that causes recurrent inflammatory attacks that preferentially target the optic nerves and spinal cord, leading to blindness, paralysis and death (Mealy, Wingerchuk, Greenberg, & Levy, 2012; Oh & Levy, 2012; Wingerchuk et al., 1999). It affects approximately 4,000-8,000 people in the United States, (Mealy et al., 2012) and has a worldwide prevalence estimated to be 0.52 to 4.4/100,000 (Marrie & Gryba, 2013). In contrast to multiple sclerosis (MS), a related CNS autoimmune disorder that primarily targets myelin, NMOSD causes irreparable neuronal cell death which leads to more severe disability and a poorer prognosis (Popescu & Lucchinetti, 2016). Historically, within 5 years of symptom onset, 60% of NMOSD patients were blind in at least one eye, 52% were weak in at least one limb requiring gait assistance and mortality was as high as 30% (Wingerchuk et al., 1999). These grim outcomes have improved since the discovery of the highly-specific anti-aquaporin-4 (AQP-4) biomarker for NMOSD in 2004 which allows clinicians to diagnose patients early and treat correctly, such that the mortality rate is now down to seven percent (Mealy et al., 2018). Even so, NMOSD continues to cause more severe permanent disability compared to MS (Wingerchuk, Lennon, Pittock, Lucchinetti, & Weinshenker, 2006; Mealy et al., 2012). Though a rare disease, NMOSD is devastating for those who have it.

Etiology of CNP in NMOSD

Despite these devastating consequences of the disease, patients have reported that pain is among the most prevalent and debilitating symptom, impacting mood, mobility and quality of life (QoL) (Qian et al., 2012; Zhao et al., 2014; Kanamori et al., 2011; Hollinger et al., 2016; Shi et al., 2016; Moore et al., 2016; Kong et al., 2016). In particular, central neuropathic pain (CNP) is pervasive, severe, intractable to treatment, and affects 62-91% of patients with NMOSD (Zhao et al., 2014; Pellkofer et al., 2013). CNP is described as distressing, persistent and incapacitating (Cohen & Mao, 2014; Dworkin et al., 2007). The presence of CNP in NMOSD is a direct consequence of targeted immune-mediated destruction of the spinal cord and may be influenced by lesion span and location: NMOSD lesions are generally transverse, involving both the central gray matter and dorsal horns (Figure 1). The dorsal horns are innervated by primary ascending fibers that convey sensory information to the brain (Zhao et al., 2014; Pellkofer et al., 2013; Bradl et al., 2014; Todd, 2010). Damage to the central gray matter in NMOSD leads to astrocytic damage and tissue necrosis, thus disrupting sensory pain tracts going to and from the brain (Qian et al., 2012; Kanamori et al., 2011). As a consequence of ongoing spontaneous activity arising in the periphery, surviving neurons develop increased background activity and increased responses to ascending nerve impulses, including normally harmless tactile stimulation (Centonze, 2014). An additional mechanism of CNP involves peripheral sensitization of non-myelinated ascending C fibers interpreted by the brain as persistent pain, a characteristic sign of an inflammatory process in the spinal cord (Pellkofer et al., 2013).

Current Treatment of CNP

Even with the increased awareness of the effects of persistent pain in patients with NMOSD, treatment is still lacking. Currently, there is no standard of care for CNP treatment. As with neuropathic pain from other etiologies, the most frequently-used medications for its treatment in NMOSD are anti-epileptics, antidepressants and non-steroidal anti-inflammatory agents. Descriptive studies in NMOSD recognized the inadequate effect of these medications, resulting in frequent breakthrough opioid use (Qian et al., 2012; Zhao et al., 2014). Consequently, doses and numbers of medications are often increased, causing side effects, particularly at higher doses, which are independently associated with fatigue (Pellkofer et al., 2013). With growing awareness of the dangers of polypharmacy, exploring non-pharmacologic interventions to use in combination with pharmacologic therapies broadens options for CNP treatment. Advancing alternative mechanisms for pain treatment, either in isolation or combined with pharmaceutical interventions, may allow for reduced medication dosing that does not exacerbate other symptoms with which the patient is already struggling.

Randomized controlled trials have demonstrated efficacy of non-pharmacologic interventions for other pain conditions, and this work has been extended to SCI and MS populations for the treatment of CNP with interventions such as nerve stimulation, acupuncture, exercise and massage therapy (Widerstrom-Noga & Turk, 2003; Boldt et al., 2014; Namjooyan, Ghanavati, Majdinasab, Jokari, & Janbozorgi., 2014). A novel technology called Scrambler therapy is a non-invasive pain modifying intervention that utilizes transcutaneous electrical stimulation of ascending C fibers with the intent of re-organizing maladaptive signaling pathways (Coyne, Wan, Dodson, Swainey, & Smith, 2013). This neuromodulatory therapy has been investigated for treatment of persistent peripheral neuropathic pain in several conditions including chemotherapy-induced neuropathy, post-

herpetic neuralgia and post-surgical neuropathic pain with promising results (Coyne et al., 2013; Majithia et al., 2016; Lee et al., 2016; Pachman et al., 2015; Smith, Coyne, Parker, Dodson, & Ramakrishnan, 2010; Ko, Lee, & Lee, 2013; Marineo, Iorno, Gandini, Moschini, & Smith 2012). Patients report sustained relief after undergoing daily treatment sessions for 10 consecutive weekdays (Majithia et al., 2016). The effect of Scrambler therapy on patients with persistent central neuropathic pain has not been systematically tested, despite anecdotal support for its use (D'Amato, Mealy, Erdek, Kozachik, & Smith, 2018; Mealy, Newsome, Kozachik, Levy, & Smith, 2018). Determining if Scrambler technology is an acceptable, feasible, and effective way to intervene on the pain experienced by those with NMOSD is the first step toward offering an enhanced QoL to functionally impaired patients (Zhao et al, 2014; Mutch et al., 2014; Moore et al., 2016). Improving functional status and QoL may afford patients with opportunities to engage in richer lives socially, personally and professionally in the context of significant pain reduction, and Scrambler potentially enables this in a non-invasive way. This research provides a unique opportunity to advocate for patients by recognizing the impact symptoms have on quality of life and exploring remediation.

Scrambler Therapy: potential application to central neuropathic pain

Scrambler therapy was granted approval by Food and Drug Administration (FDA) 510(k), "Scrambler ST 5 TENS Device," (K081255) in February 2009 for acute, chronic and post-operative pain (https://www.accessdata.fda.gov/cdrh_docs/pdf8/K081255.pdf, 2009). Scrambler is a type of transcutaneous electrostimulation (TENS) that uses peripheral nerve stimulation to modify ascending sensory responses in the spinal cord. Electrical impulses are transmitted via surface electrodes placed surrounding the pain area (Figure 2). Traditional

TENS units take advantage of the Gate Control Theory in which stimulation of surrounding A-delta fibers dampens incoming pain signals (Garrison & Foreman, 1994; Blivis, Haspel, Mannes, O'Donovan, & Iadarola, 2017). Scrambler therapy provides additional stimulation of ascending sensory C fibers that imitate normal nerve action potentials with the intent of re-organizing maladaptive signaling pathways (Coyne et al., 2013). The theory behind Scrambler treatment is that "scrambled" waveforms – instead of repetitive identical waveforms in traditional TENS – are dynamically assembled into strings of information that are interpreted by the brain to replace pain with "no-pain" information (Majithia et al., 2016; Ricci et al., 2012). In contrast to traditional TENS therapy that provides only short-term pain relief, studies with Scrambler therapy in peripheral neuropathy suggest that patients can have significantly reduced pain or be pain-free for up to 3 months following a series of treatments, and that follow-up treatments may require fewer sessions for continued relief (Majithia et al., 2016).

Use of Scrambler therapy for neuropathic pain management has been reported in 28 peer-reviewed articles in peripheral neuropathic pain syndromes (Majithia et al., 2016; Smith, Cheville, Loprinzi, & Longo-Schoberlein, 2017; Joo, Cho, Cho, Kym, & Seo, 2017; Park et al., 2017; Kim, Lee, & Lee, 2017; Kashyap, Joshi, Vig, Singh, & Bhatnagar, 2017; Smith, Auwaerter, Knowlton, Saylor, & McArthur, 2017). In the largest sample to date (n=226), 80% of patients had a greater than 50% reduction in pain in a prospective, open-label trial (Sabato, Marineo, & Gatti, 2005). The most studied condition has been chemotherapy-induced neuropathy and other cancer-related pain (Lee et al., 2016; Pachman et al., 2015; Coyne et al., 2013; Smith et al., 2010; Ricci et al., 2012; Park et al., 2013; Notaro et al., 2016), where Scrambler has provided significant pain reduction in all but one randomized

study which found no difference in a small sample size (n=14) (Campbell et al., 2013). The only other trial conducted with an equally rigorous prospective double-blinded placebo-controlled design was for the diagnosis of low back pain (n=30) where the treatment group was found to have a significant reduction in pain compared to the control group (Starkweather et al., 2015). No serious adverse events have been reported related to treatment with Scrambler therapy (Majithia et al., 2016). In central neuropathic pain, the damaged neurological circuits reside in the spinal cord rather than the peripheral nerve. However, the stimulation via electrodes is to dermatomes that correspond to intact spinal cord tissue, on which the Gate Control Theory and Scrambler mechanisms are thought to act.

NMOSD as a Translational Model for Treatment of CNP from other Causes

NMOSD is an ideal disease in which to test a proof-of-concept intervention for pain. First, there remains a significant unmet need for pain treatment in NMOSD as current medical and non-medical interventions have had little impact (Zhao et al., 2014). Second, the severe pain associated with NMOSD allows for even subtle improvements to be detectable. The damaged spinal cord circuits in NMOSD are similar to the pathologies in related CNP etiologies including traumatic spinal cord injury and MS. If a tested treatment is found to be effective at improving CNP in the NMOSD patient population, it may also be useful in these related conditions. CNP is associated with worse overall health in all diseases, and is difficult to treat (Cohen & Mao, 2014; Dworkin et al., 2007).

Specific Aims and Hypotheses

The aims for this study were as follows:

Aim #1: To examine the safety, feasibility, acceptability and effectiveness of Scrambler therapy in treating central neuropathic pain in NMOSD. Hypothesis 1: Scrambler therapy is a safe, feasible, acceptable and effective intervention.

- Sub-aim #1a: Feasibility of treatment was examined to determine whether the intervention was appropriate for this patient population, toward the effort of informing a larger, Phase III study. This was measured by assessing the following: 1) adherence to visit schedule and 2) response to the following question asked directly after completion of the 10-day treatment period: "Do you think you received treatment?" (Yes/No). Acceptability was measured by assessing response to the following question, also asked directly following the treatment course: "Would you want to continue treatment in clinic, if available?" (Yes/No).
- Sub-aim #1b: Safety was be measured based on a comparison of safety profiles in treatment versus sham arms.
- Sub-aim #1b: Effectiveness was evaluated based on degree of improvement of pain using an 11-point Numeric Rating Scale (NRS) score in the treatment group compared to sham, with the primary outcome focused on end-of-treatment time point, and the secondary outcomes examined sustainability of effect at 30- and 60-days following treatment.

Aim #2: To assess the relationship between improved pain in response to Scrambler therapy and other co-occurring symptoms, including anxiety, depression and sleep disturbance, in patients with NMOSD. Hypothesis 2: Impacting pain with Scrambler therapy will also improve some or all co-occurring symptoms.

Aim #3: To investigate components of the symptom cluster in patients with NMOSD and the influence of pain on co-occurring symptoms and QoL. Hypothesis 3.1: Pain will be associated with QoL and co-occurring symptoms including anxiety, depression and sleep disturbance, in patients with NMOSD.

Innovation

First study to investigate an intervention for pain in patients with NMOSD

Despite the significant unmet need in NMOSD, there have been no trials in this patient population investigating any pharmacologic or non-pharmacologic intervention for pain management in the United States. Given that most patients are currently on medications commonly used for peripheral neuropathic pain treatment, this proposal utilized a multimodal approach that combines a non-pharmacological intervention with more-established pharmacological agents. Targeting co-occurring symptoms using a multimodal approach (incorporating multiple interventions that have different mechanisms of action) may be more effective in improving symptoms, and consequently, QoL. A multimodal approach impacts QoL more robustly in comparison to a unimodal intervention in related autoimmune diseases of the central nervous system (Crayton & Rossman, 2006; Turcotte et al., 2015). The current proposal implements the multimodal use of Scrambler therapy added to a stable pharmacologic regimen to increase the likelihood of successfully treating pain and, in turn, positively impacting QoL.

Scrambler Therapy is a novel, non-invasive approach for treatment of central neuropathic pain from any cause

Despite the growing body of evidence to support efficacy of Scrambler, the utility of Scrambler therapy for treatment of CNP pain has never been systematically explored prior to this investigation. As in peripheral neuropathy, the expectation was that Scrambler therapy would act as a neuromodulator by providing new, non-painful sensory signals that replace the previous nociceptive signals, which get interpreted by the brain. Similar to how the brain interprets sensory impulses as pain after spinal cord damage occurs, neuroplasticity within the central nervous system enables retraining of that perception of pain so that the area of concern is no longer interpreted by the brain as painful. The Scrambler device has pre-market clearance through the FDA for acute, chronic and post-operative pain, and is not restricted to peripheral neuropathy (https://www.accessdata.fda.gov/cdrh_docs/pdf8/K081255.pdf, 2009).

Preliminary Data

Scrambler Therapy for Central Neuropathic Pain

We have recently treated and published results for two patients with central neuropathic pain with Scrambler: one with longstanding CNP as a consequence of a brainstem stroke (D'Amato et al., 2018), and the second with transverse myelitis (Mealy et al., in press). CNP in both patients was previously unresponsive to multiple neuropathic pain agents, and each underwent 10 days of Scrambler treatment. The patient with the brainstem stroke had a reduction in her pain from 9-10/10 to 0-0.5/10, and she was able to discontinue all pain medications. The patient with transverse myelitis is further described below in detail. In both cases, we started Scrambler treatment at Day 1 with electrodes placed above the affected dermatome (which corresponds to lesion level), and lowered channel-pairs daily as pain level declined down the body, corresponding to the spinal cord level. These two cases

offer proof-of-concept for the treatment of CNP through Scrambler therapy and have informed the current proposal.

Case presentation. A 65-year-old Caucasian woman with history of TM presented with long-standing central neuropathic pain. She was initially evaluated at an outside hospital in October 2013 for right hand paresthesias with accompanying neck pain followed by lower extremity weakness, right arm incoordination and weakness, urinary retention, torso band-like tightness, and impaired ambulation. Progression to nadir developed over approximately 24 hours. Neuroaxial imaging showed a C3-5 lesion on T2-weighted sagittal and axial sequences with mild ill-defined peripheral enhancement on post-gadolinium T1-weighted sequences (Figure 4). Mild stenosis and foraminal narrowing was noted, though flexion/extension X-rays indicated preserved cerebrospinal fluid signal surrounding the cord. No flow voids were noted. Given the MRI findings in the setting of symptoms attributable to the described lesion, presence of a sensory level, progression to nadir between 4 hours and 21 days, the presence of oligoclonal bands, and a thorough autoimmune evaluation to rule out other causes, the diagnosis of TM was made in concordance with the TM Consortium Working Group diagnostic criteria (2002). Muscle and nerve conduction studies were conducted and were unremarkable. The patient underwent 5 days of high-dose corticosteroids with modest improvement in her neurologic status.

She presented to the Johns Hopkins Transverse Myelitis Center in April 2014 for a second opinion due to persistent weakness and severe neuropathic pain. Neurologic exam demonstrated diffuse hyperreflexia, mild left hip flexion weakness, and gait dysfunction. In depth interview revealed that her neuropathic pain (in her bilateral legs, and right arm and torso) was the most disabling aspect of her condition. She was on hydrocodone-

acetaminophen (5-300 mg every 6 hours as needed) and tramadol (50 mg every 4 hours as needed) prior to presenting to us which was only partially beneficial. Subsequently, she tried several other therapies that were ineffective, only partially helpful or caused intolerable side effects, including duloxetine (120 mg daily), gabapentin (900 mg three times daily), pregabalin (50 mg twice daily), nortriptyline (50 mg daily), capsaicin, topical lidocaine, meditation and acupuncture. In early 2017, she was offered Scrambler therapy for refractory pain treatment. At the time of Scrambler treatment, she was on duloxetine (120 mg) daily and topical lidocaine as needed. The patient received Scrambler therapy for 45 minutes daily over a period of 10 consecutive weekdays, the typical administration as delivered for other types of pain (Calmare Technologies Inc., 2008). Prior to initiation of Scrambler treatment, the patient reported a pain level of 5 out of 10 using an 11-point (0-10) numeric rating scale (NRS) in the morning, which would increase to an NRS pain level of 10 out of 10 by nighttime, as well as with exertion and stress. She had developed activity intolerance secondary to pain. The neuropathic pain was located in the regions mentioned above and she reported severe allodynia in her right upper extremity that interfered with her grip. Moreover, the pain interfered with sleep.

The stated purpose of Scrambler Therapy is to provide “non-pain” information to replace continued pain-generation impulses. To do this requires capturing the surface receptors of the C fibers (and perhaps other fibers) in the dermatome of the affected nerves. The placement is done to also avoid putting an electrode directly on an area of damaged nerve sensation. This patient’s worst pain was in the C-6,7,8 distribution and involved the distal arm to the axilla; she also had pain in the T-1, and L5 distribution. To begin, we placed sets of electrodes (“channels”) in the C6 and C8 dermatomes in an area of normal sensation, about

8 inches apart, being careful to stay above the area of distal allodynia and pain (Figure 5). At end of Day 1 treatment, her NRS scale pain score decreased to 1 out of 10 and her allodynia was improved. By Day 2, the pain had returned to 3/10, but the pain/allodynia area had moved down the arm, such that we could treat with pairs of electrodes on C6, C7, T8 with the distal lead on the medial arm for C8, and L5 to L5. At end of Day 2 treatment, the score decreased to 1.5 out of 10, with resolution of banding sensation and shoulder/upper arm pain. On Day 3, her pain score started at 2 out of 10. All five channel-pairs of electrodes were used, each spanning across one of the following dermatomes: C6, C7, C8, T8 and L5. The patient continued with all five channel-pairs for the duration of treatment. Prior to beginning treatment on Day 4, her pain score was reported at 4 out of 10, and 0 out of 10 by end of treatment; of note, allodynia had completely resolved. Her pain continued to decline in severity and in location daily following each treatment, with the pain being nearly resolved by the end of Day 10 (Figure 6). The patient reported no adverse events.

In the 30 days following Scrambler intervention, the patient's pain remained improved, with a pain score of 2.5 out of 10. Furthermore, her sleep and activity intolerance improved. Over 90-day follow-up, her pain began to increase to pre-treatment levels. However, the patient reported that Scrambler therapy helped in reducing her pain more than any previous therapy and expressed a desire to receive another course of treatment.

Our patient experienced persistent central neuropathic pain for 3.5 years prior to Scrambler therapy and reported that this treatment improved her pain considerably more than previous pharmacologic and non-pharmacologic interventions. The patient further recounted that this treatment was tolerable, and no safety concerns have emerged in our patient or others treated with Scrambler (Majithia et al., 2016). Our patient's re-emergence of pain at

approximately 90 days, mirrors data from Scrambler use in peripheral neuropathic pain conditions. Observational research suggests that patients who receive subsequent treatments continue to respond to additional treatments, often with fewer treatments needed over time (Smith et al., 2017; Smith et al., 2017). Scrambler therapy is an emerging non-invasive treatment that may be safe and effective for central neuropathic pain. Notably, most reports of Scrambler use have been observational, in which the impact of placebo effect could not be accounted, including in the current report. Nonetheless, this open-label case report supports comprehensive, well-controlled investigation of Scrambler therapy in MS, NMOSD and other disorders that cause refractory central neuropathic pain.

Symptom co-occurrence in NMOSD and the effect on QoL

A symptom cluster is a group of interrelated co-occurring symptoms in a given chronic disease (Kim, Abraham, & Malone, 2013). Recent research investigating symptom clusters in other chronic diseases suggests that treating one symptom among a cluster does not sufficiently improve QoL (Kim, et al.; 2013). The implication for NMOSD is that treating CNP in isolation may not be sufficient to improve QoL in the context of other debilitating symptoms including anxiety, depression and sleep disturbance. In MS, which presents with similar symptoms as in NMOSD, the complexity and interconnectedness of symptoms seems apparent in the research: pain has been shown to affect anxiety and depression, as well as QoL (Archibald et al.,1994; Alschuler, Jensen, & Ehde, 2012); sleep is an independent predictor of QoL (Merlino et al., 2009) and sleep difficulties exacerbate other MS symptoms (Manocchia, Keller, & Ware, 2001); sleep disruption may contribute to the development of depression (Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Manocchia et al. 2001); pain impacts depression and is mediated by anxiety, sleep quality and fatigue (Amtmann et al.

2015). This suggests that addressing one symptom may also impact other co-occurring symptoms. Drawing from the MS literature, if the presence of pain in NMOSD impacts depression, anxiety and sleep disturbance, then adequate treatment of pain could have an impact on these other symptoms. This may be particularly true in NMOSD, given that the pain is more severe than in MS and published data suggest that pain disproportionately impacts QoL in NMOSD as compared to other co-occurring symptoms (Mealy, Simpson, Levy, 2016; Mealy et al., 2017).

In NMOSD, pain correlates with anxiety, depression and disability, and is associated with poorer QoL (Moore et al., 2016). Interestingly, poor QoL does not correlate with disability, anxiety or depression. Taken together, these findings support our own findings which suggest that, while symptom co-occurrence exists in NMOSD, adequate pain treatment may improve these symptoms and, in turn, QoL (Table 1). The evidence for co-occurrence of symptoms provides preliminary evidence for the need to explore the presence of a symptom cluster. Exploring the presence of a symptom cluster and the impact of pain on co-occurring symptoms may influence approaches to treatment in the future. The Theory of Unpleasant Symptoms (TOUS) provides the theoretical underpinning for such an analysis (Figure 3). TOUS postulates that co-occurring symptoms are both influenced by and influence physiologic, psychologic, and situational factors, with a combined or synergistic effect on the outcome (Lenz, Pugh, Milligan, Gift, & Suppe 1997). Analyzing the effect of pain treatment on QoL will offer providers more information about how to approach symptom management in this population.

Measuring Pain in NMOSD

A number of measures that have been developed for pain assessment have been used for research in patients with neuroimmunologic disorders, particularly in MS, and include the Visual Analog Scale (Khan F, Amatya B, & Kesselring, 2013), Numeric Rating Scale (NRS; Svendsen, Jensen, & Bach, 2004), McGill Pain Questionnaire (MPQ; Silver, Blum, Grainger, Hammer, & Quessy, 2007) and the Brief Pain Inventory (BPI; Vollmer, Robinson, Risser, & Malcolm, 2014). However, the nature of the pain experienced by NMOSD patients is exceptional in its chronicity and intensity. Three pain instruments have been utilized to better elucidate our awareness of pain in NMOSD, the NRS (Qian et al., 2012; Pellkofer et al., 2013; Araki et al., 2014; Ringelstein et al., 2015), MPQ (Qian et al., 2012) and BPI (Kanamori et al., 2011; Zhao et al., 2014) none of which has yet been validated for use in this population.

Potential Application of Brief Pain Inventory in NMOSD

A synthesis of the literature was performed to investigate clinical and research utility of the BPI, as well as evidence for reliability and validity of the measurement tool. Specifically, this synthesis aimed to describe the inception, development, reliability and validity of the BPI across diseases, and its use in nursing literature, with the singular purpose of assessing its applicability in NMOSD. A PUBMED search was conducted that specified "Brief Pain Inventory," AND "reliability," "validity" and/or "validation" in the title/abstract. Eighty-one articles were found that addressed reliability and validity of the instrument. Because of the focus of the current synthesis on NMOSD, only those validation studies that were pivotal to the tool's inception and development and/or pertinent to use in NMOSD were included. For its use in nursing research, a broad search of the Cumulative Index of Nursing and Allied Health Literature (CINAHL) Plus database was conducted using the search term

"Brief Pain Inventory" in all text and narrowing by "Nurse" as Any Author, which provided 27 articles for review. Articles were not limited by date for either search. The BPI User Guide was additionally used as a reference.

Description of BPI and current research. According to the Brief Pain Inventory User Guide, the BPI was originally conceptualized in the late 1970's in response to the need for better capture of the severity and impact of cancer pain and as a way to quantify improvement in pain after changes to analgesic therapy were made (Cleeland 2009). This was an initiative of the National Cancer Institute (NCI) and World Health Organization (WHO), in response to growing awareness of the incapacitating pain associated with cancer. At the time, existing questionnaires including the MPQ mostly sought to assess nonmalignant pain and were thought to be too burdensome for patients suffering from severe intractable pain; they were lengthy, complex and included irrelevant items. Patients were asked what questions they felt were the most important for communicating their pain experience, and it became clear that no such tool existed. Supported by NCI and WHO, the Pain Research Group at the University of Wisconsin Medical School-Madison, under the direction of Charles S. Cleeland, PhD, planned a program to develop a self-report instrument that would be short, easily-understandable, could be self-administered, could be easily translated into other languages, and, importantly, would capture not only pain severity, but also the perception of how pain affected daily life. This group later became the Department of Symptom Research at The University of Texas MD Anderson Cancer Center (Cleeland., 2009).

Several iterations of this instrument were attempted over the years to ensure that the tool captured the data intended by the group, in the way they intended to capture it, as outlined above. According to Cleeland (2009), the working group eventually came up with

the BPI long form, followed by the short form. The BPI short form shortened the recall period from 7 days to 24 hours for question reference, and is generally the form that is being referenced when simply citing the "BPI". It is comprised of front and back body diagrams, four pain severity items and seven pain interference items rated on 0–10 scales, and a question about percentage of pain relief by analgesics. Each section is first scored individually for the self-administered current version. The BPI assesses pain severity in four questions from pain at its "worst," "least," "average," and "now" (current pain). Pain interference is measured among seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. BPI pain interference is typically scored as the mean of the seven interference items. This mean can be used if more than 50%, or four of seven, of the total items have been completed on a given administration. While other items exist on this measurement tool, they are at this time supplemental and do not contribute to the scoring as they have not been validated or proven useful in the context of the tool as a whole. The fee for use is dependent on the intended use: unfunded academic research is able to obtain for free, $300 for funded academic research, and significantly more for commercial research at $2,000. Also, the language may influence price (Cleeland, 2009).

Evidence of BPI reliability and validity. The BPI was initially devised for cancer pain and initial reliability and validity testing was performed in this English-speaking population; Cronbach's alpha reliability ranges from 0.77 to 0.91 and test-retest reliability for ratings of pain "worst" (0.93) and "usual" or "average" pain (0.78) in patients with cancer was high, which signals acceptable reliability (Daut, Cleeland, & Flanery, 1983; Cleeland et al., 1994). As expected, test-retest reliability for pain "now" severity ratings were lower (0.59) since pain intensity changes over time (Daut et al., 1983). Exact validity testing

performed in the initial English-speaking cancer pain patient sample could not be reported as only the abstract was available. However, the measurement tool has since been validated for use in peripheral neuropathy (Wu et al., 2007), chronic non-cancerous pain (Dworkin et al., 2008), post-herpetic neuralgia in herpes zoster (Coplan et al., 2004), spinal cord injury (Bryce et al., 2007), inguinal pain following hernia repair (Franneby et al., 2008), osteoarthritis (Kapstad, Hanestad, Langeland, Rustoen, & Stavem, 2008), and cerebral palsy (Tyler, Jensen, Engel, & Schwartz 2002), to name several. Additionally, it has been validated psychometrically and linguistically in over 20 other languages and has been linguistically validated in another thirty (Cleeland, 2009). It has been proposed that the BPI should be utilized in all clinical trials involving chronic pain (Dworkin et al., 2008).

Many studies in MS have used the BPI over the years (Osborne, Raichle, Jensen, Ehde, & Kraft, 2006; Newland, Naismith, & Ullione, 2009; Newland, Riley, Fearing, Neath, Gibson, 2009). Osborne et al. specifically addressed reliability and validity of this instrument in MS patients with chronic pain and aimed to examine psychometric properties of interference measures only (Osborne et al., 2006). As such, only the interference component of the BPI was utilized and was administered to MS patients by mail. The modified BPI interference scale demonstrated excellent internal consistency (α=0.93-0.96) as well as construct and concurrent validity, providing preliminary support for the reliability and validity of this modified scale for use in MS patients with chronic pain. Construct validity was assessed by factor analysis. The principal factor analysis examining the items from the modified 10-item version of the BPI Interference scale and the three pain intensity items also resulted in a two-factor solution that was rotated with direct oblimin. The first factor accounted for 64.6% of the variance and the second factor accounted for an additional 9.2%

of the variance. All 10 interference items had high factor loadings on Factor 1 (range 0.59 to 0.94) assessed by correlation analyses to examine the associations between the pain interference items and scale scores and the measures of pain intensity and psychological functioning. Pearson correlation coefficients indicate that the first seven items from the BPI Interference scale were each significantly associated with average pain intensity, with correlations ranging from 0.42 to 0.69.

A study out of Turkey examined the psychometric properties of the BPI as well as its reliability, validity and discriminative utility for estimating the status of chronic pain in neuropathic and nociceptive pain (Erdemoglu & Koc, 2013). Patients with chronic pain were evaluated by a pain specialist and the etiology of their pain was determined to be either nociceptive or neuropathic. Test-retest was done for everyone, and no significant differences were found between the two tests within the nociceptive and neuropathic groups (Cronbach's α for test=0.84 and retest=0.83). Cronbach's α was performed for reliability testing of pain interference items, and the internal consistency between items was relatively high for all groups (7 items each for each of two groups, ranging from 0.61-0.81). Principal component analysis yielded three factors (severity scale, activity interference, and sleep and mood interference) which explained 70.68% of the variance for the nociceptive group and 66.48% for the neuropathic group. The component of the study, which utilized a composite score based on BPI and another pain measure, looked at differentiating pain. As nociceptive pain is not an important component of the pain syndrome found in NMOSD, this will not be reported for the purpose of this critique.

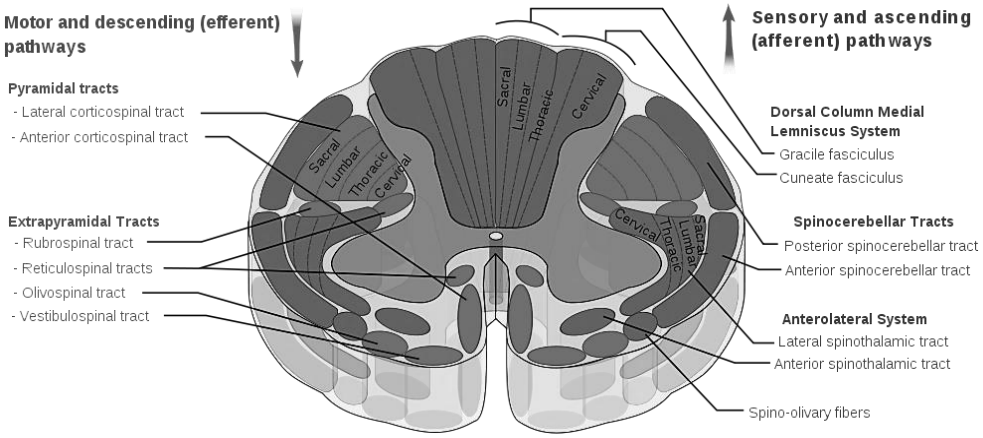
Use in nursing research. Twenty-seven articles were found that involved nursing research utilization of the BPI. Not surprisingly, the bulk of nursing research explored

different aspects of cancer pain (11 manuscripts). Another three manuscripts examined post-operative pain, two looked at fibromyalgia, two addressed MS and the remaining nine each had one article on a variety of topics. None of these addressed validation of the measure in the given population and instead utilized the BPI to measure pain in their cohorts. Given the relevance to the topic at hand, a closer look was taken at the two MS studies. The first assessed pain, fatigue, depression, sleep disturbance and quality of life in women with MS compared with healthy controls (Newland et al., 2009). The researchers utilized the BPI-long form, in addition to the MPQ. While the study does not explicitly discuss the rationale for choosing these two instruments, the authors state that the two instruments have been concurrently validated previously by Ehde, Nitsch, & Smiley (2015). These authors found that while pain interfered with fatigue, depression and sleep in both women with MS and healthy controls, those with MS had significantly more chronic pain characterized by severe intensity and significant pain-related interference with activities. The second study is a secondary analysis that examines relationships among pain and demographic variables in women with MS, such that demographic factors other than sex could be explored (Newland et al., 2009). It also utilizes both the MPQ and BPI-long form. The authors explain that they used the MPQ to investigate pain prevalence while the BPI-long form examines interference and intensity. Women with MS with higher education levels were found to have lower prevalence, interference and intensity, than those less educated. Furthermore, employment was positively associated with decreased pain prevalence in the MS group. These findings suggest that less educated and unemployed women with MS are at increased risk to experience pain, according to the authors.

Discussion. We found no evidence of reliability or validity testing of the BPI in NMOSD cohorts. The BPI addresses chronic pain in particular and includes items specific to pain severity as well as pain interference in a person's life. Given the evidence to support that the quality of life in NMOSD patients is profoundly affected by pain, it seems advantageous to utilize a measure that recognizes and evaluates both of these aspects of pain. Like with cancer pain, being able to quickly and easily assess multidimensional features of pain is ideal in a population such as NMOSD because of the chronicity and severity of the pain that exists.

In contrast to MS which predominantly affects Caucasians of northern European ancestry (Ontaneda, Hyland, & Cohen, 2012), NMOSD disproportionately affects non-whites, particularly those of Asian and African descent (Mealy et al., 2012). Exploring validation of this measure in other languages with a high prevalence of NMOSD would be of value. NMOSD also disproportionately affects women at very high rates (6.5-9:1) (Mealy et al., 2012; Jarius et al., 2012). No testing particular to any one gender or sex was discovered during the literature review of the BPI. Research suggests that perception of and responses to pain differ by sex (Bernardes, Keogh & Lima, 2008; Rahim-Williams et al., 2012). This discrepancy is supported by Zhao's findings in NMOSD, where 72% of women compared to 27% of men reported pain (Zhao et al., 2014). Evaluating if responses differ by sex or whether the BPI is more sensitive in capturing pain in one sex versus the other would be of value. In conclusion, the BPI has excellent face validity for application in NMOSD and future research directed at establishing its reliability and validity in this population would prove useful.

Figure 1. Cross-section of the spinal cord depicting spinal tracts.



From: https://commons.wikimedia.org/w/index.php?curid=10909281.

Figure 2. A picture of the GEOMC Pain Scrambler model MC-5A with electrode placement.

Permission from Thomas Smith, MD

Figure 3. Theory of Unpleasant Symptoms (Lenz et al., 1997)

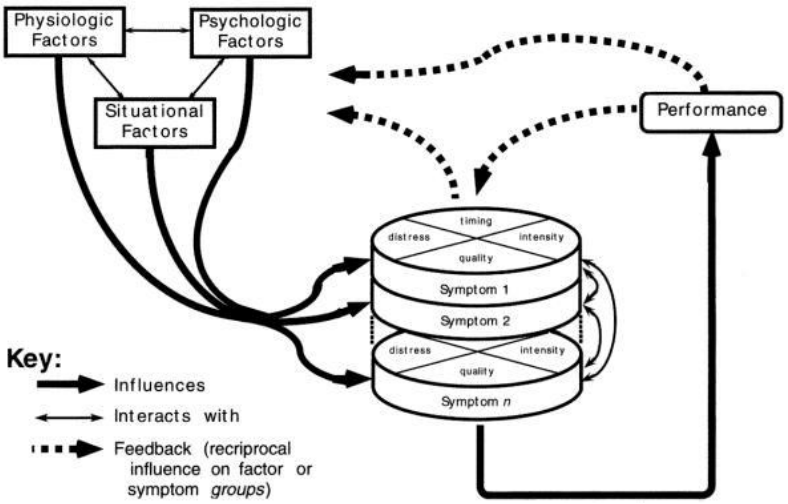


Figure 4.

MRI imaging showing C3-5 lesion following presentation of symptoms:

A. T2-weighted sagittal

B. T2-weighted axial

C. T1-weighted sagittal post- gadolinium

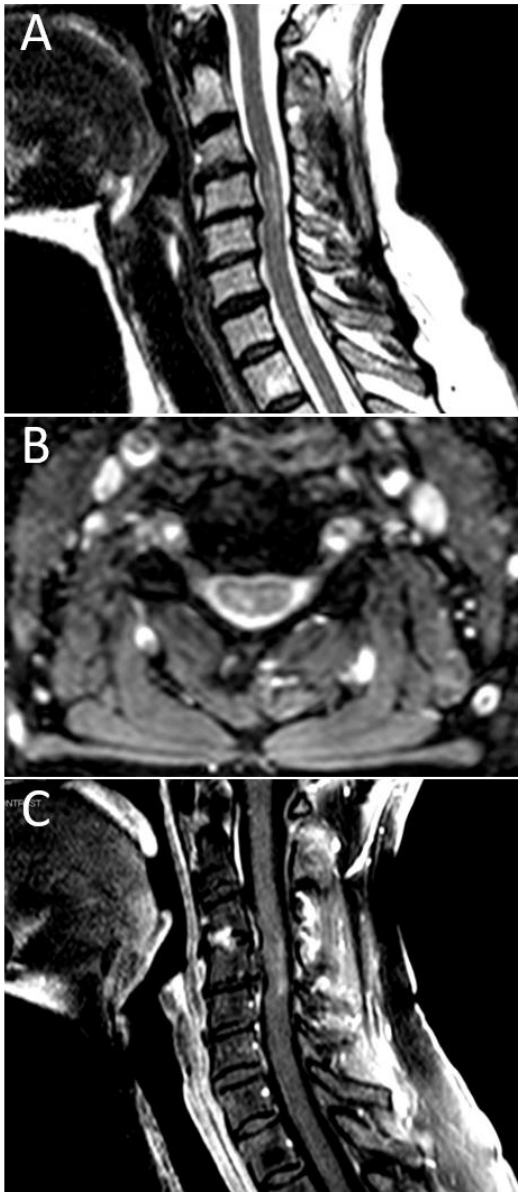
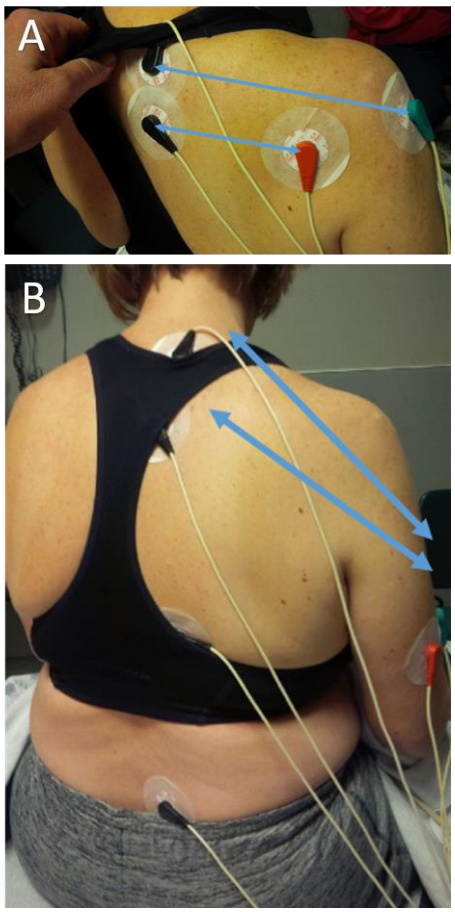


Figure 5.

A. Electrode placement for Day 1 targeting the C6 distribution, and a second pair spanning over the C8 distribution.

B. Due to decrease in the anatomic pain level, the electrode pairs were lowered to the dermatome that corresponded with C7 on Day 2. Two other electrode pairs were placed at C8-T1, and L5-L5.



Acknowledgement

The patient provided written permission to share her story and photographs for educational purposes.

Figure 6.

NRS pain scores, daily pre- and post-treatment and at indicated follow-up intervals.

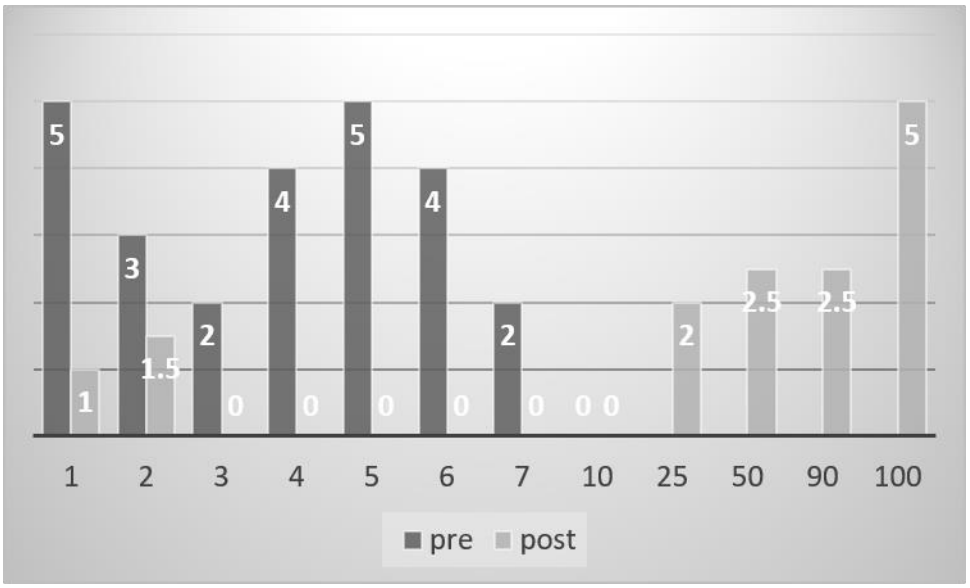


Table 1: Preliminary research to support Aim 3.

Type of investigation	**Aim**	**Outcome**
Cross-sectional descriptive study (Mealy et al., in press)	To assess the prevalence and relationship among common symptoms in NMOSD	➢ In a multivariate model that included measurement of pain, fatigue, depression, and functional disability, only pain was a significant predictor of the overall QoL, when controlling for all other variables (p=0.0068). ➢ Upon further exploration into the impacts on QoL, individual EQ5D items were examined, and high burdens were discovered among all five items; anxiety/depression (66.6% experienced at least some problems), pain/discomfort (75.0%), and mobility (65.2%) were the best predictors of poor QoL.
Cross-sectional exploratory descriptive study (Mealy, Simpson, Levy, 2016)	To contrast symptom presence and co-occurrence in NMOSD and MS	➢ Patients with NMOSD had more disability and pain than did patients with MS via t-tests. ➢ Pain was the only symptom that was independently associated with all other symptoms via linear regression (p<0.05).

Chapter 2: Review of treatment for central spinal neuropathic pain and its effect on quality of life: implications for neuromyelitis optica spectrum disorder (Manuscript 1)

Maureen A. Mealy, RN, PhD(c)

Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Sharon L. Kozachik, RN, PhD

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Michael Levy, MD, PhD

Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA

Abstract

Neuromyelitis optica spectrum disorder (NMOSD) causes disabling and persistent central neuropathic pain (NP). Because the pain syndrome in NMOSD is severe and often intractable to analgesic treatment, it interferes with quality of life in patients. No interventional trials have been published looking at response to interventions for pain in NMOSD. This is a synthesis of the literature surveying the impact on quality of life of interventions in all mechanisms of central spinal NP. This review has important implications for management of pain in NMOSD. A systematic database search was conducted using Pubmed, Embase and CINAHL Plus with keywords including "spinal cord," "quality of life" and "neuropathic pain" in an attempt to identify original research that targeted spinal NP treatment and used quality of life as an outcome measure. Both pharmacologic and non-pharmacologic treatments were sought out. Twenty-one studies meeting our eligibility criteria were identified and evaluated, 13 using pharmacologic treatments and 8 using non-pharmacologic interventions. Overall, sample sizes were modest, and effects on decreasing pain and/or improving quality of life were sub-optimal. This review provides researchers with a foundation from which to start a more thorough and thoughtful investigation into the management of NP in NMOSD and underscores the importance of including quality of life as a clinically meaningful outcome measure.

Keywords: neuromyelitis optica; neuropathic pain; quality of life, multiple sclerosis, spinal cord injury; chronic pain

Review of treatment for central spinal neuropathic pain and its effect on quality of life: implications for neuromyelitis optica spectrum disorder

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disorder of the central nervous system (CNS) that preferentially targets the spinal cord and optic nerves, leading to blindness, paralysis and death. NMOSD disproportionately affects non-Caucasians and females (Mealy, Wingerchuk, Greenberg & Levy, 2012; Jarius et al, 2012), and has a worldwide prevalence estimated to be 0.52 to 4.4/100,000 (Marrie & Gryba, 2013), affects approximately 4,000-8,000 people in the US, with a wide range of disease age at onset from infancy through old age (Mealy, et al., 2012; Jarius et al, 2012). In contrast to multiple sclerosis (MS) which primarily targets myelin, NMOSD causes irreparable neuronal cell death which leads to more severe disability and a poorer prognosis (Popescu & Lucchinetti, 2016). Historically, within five years of symptom onset, 60% of NMOSD patients were blind in at least one eye, 52% were weak in at least one limb requiring gait assistance and mortality was as high as 30% (Wingerchuk, Hogancamp, O'Brien & Weinshenker, 1999), though those data have improved with the identification of the highly specific AQP4 antibody (Wingerchuk, Lennon, Pittock, Lucchinetti & Weinshenker, 2006; Mealy et al., 2018).

NMOSD causes severe, persistent pain which is more prevalent (83.8%-91%) than in MS (~47%) (Kanamori et al., 2011; Qian et al., 2012; Pellkofer et al., 2013) and most other neurological diseases (Borsook, 2012). The most common type of pain in NMOSD is central neuropathic pain (CNP), which is characterized as agonizing burning, shooting, tingling, lancinating, and squeezing sensations that are distressing, persistent and debilitating. Half of patients with NMOSD characterize their CNP as severe and two thirds report constant pain

(Zhao, Mutch, Elsone, Nurmikko, & Jacob, 2014; Pellkofer et al., 2013). CNP typically presents weeks to months after the cord damage has occurred long after the acute injury, and may be a result of secondary changes due to reorganization of the damaged circuits of the somatosensory system (Sjolund, 2002). The pain can persist for years, decades or throughout the patient's life. The presence and severity of pain in NMOSD may be influenced by lesion span and location: NMOSD lesions are generally transverse, involving both the central gray matter and dorsal horns. The dorsal horns are innervated by primary afferent fibers and contain a large number of excitatory (glutamatergic) and inhibitory (GABA (γ-aminobutyric acid)-ergic or glycinergic) interneurons, as well as projection neurons that convey sensory information to the brain (Todd, 2010; Bradl et al., 2014). Damage to the central gray matter in NMOSD leads to astrocytic damage and tissue necrosis, thus disrupting sensory pain tracts going to and from the brain (Qian et al., 2012; Kanamori et al., 2011). As a consequence of ongoing spontaneous activity arising in the periphery, surviving neurons develop increased background activity and increased responses to ascending nerve impulses, including normally harmless tactile stimulation (Centonze, 2014).

Because many provider visits are dedicated to assessment and treatment of the underlying neurological disease, treatment of CNP is lacking despite increasing awareness of its impact on quality of life (QoL). Table 1 shows a comprehensive overview that includes seven studies assessing pain and QoL in NMOSD to date, none of which focus on an intervention or treatment. However, three studies have found promising results when examining pain as a secondary outcome, two in patients receiving a humanized monoclonal antibody that targets interleukin(IL)-6 for disease suppression, (Araki et al., 2014; Ringelstein

et al., 2015) and one in patients receiving low-dose mycophenolate mofetil (Huang et al., 2018), though none of these studies investigated QoL outcomes.

Research on the impact of persistent pain on QoL in NMOSD has found that those patients with CNP experience more depression, less enjoyment of life, and more difficulty with ambulation (Mutch et al., 2014; Pellkofer et al., 2013; Zhao et al., 2014). CNP is particularly resistant to most currently available treatments (Qian et al., 2012; Zhao et al., 2014). The most common medication classes for the treatment of CNP, used off-label, are anti-epileptics, anti-depressants and non-steroidal anti-inflammatories, but many patients still require frequent opioid use (Qian et al., 2012; Zhao et al., 2014). Cannabinoids have been recently considered for CNP as they become more available for use, though no data specific to this population have been analyzed. Despite this analgesic armament, NMOSD patients continue to have pain, in contrast to nearly half of MS patients treated for their CNP who report being pain-free (Qian et al., 2012).

Another factor to consider is that the medications used for treatment of CNP have side effects, particularly at higher doses, and are independently associated with slower reaction times and fatigue (Qian et al., 2012). Acknowledging that randomized control trials have demonstrated efficacy of non-pharmacologic interventions for other pain conditions, researchers have sought to extend this work to SCI and MS populations for the treatment of CNP, with interventions such as nerve stimulation, acupuncture, exercise and massage therapy (Widerstrom-Noga and Turk, 2003; Boldt et al., 2014; Namjooyan et al., 2014). These studies are limited by small sample size and the potential bias of symptom self-report, and they often include therapies not generally covered by insurance.

Despite research of both pharmacologic and non-pharmacologic interventions in CNP, as well as research suggesting that CNP impacts QoL, few studies have specifically examined whether a given intervention that targets pain has any side benefit on QoL. This review sought to extract, evaluate, and synthesize the literature regarding the impact of CNP interventions on QoL. This review is subdivided by pharmacologic and non-pharmacologic interventions. As no such literature exists specifically in NMOSD, central spinal pain was sought out broadly and included related conditions including MS and spinal cord injury of multiple etiologies.

Methods

A research review was conducted by performing database searches of Pubmed, Embase, and CINAHL Plus. Search terms included "neuropathic pain" and "quality of life" for each search, and the terms "spinal cord," "myelitis" and "multiple sclerosis" were each independently added to these terms in an effort to capture a comprehensive look at all causes for central NP of the spinal cord; this generated 975 citations (202 Pubmed, 721 Embase, 52 CINAHL). Results were further limited to articles and book chapters, human subjects, English language, by adding to the search "treatment" OR "intervention" OR "therapy" and by searching for "pain" specifically in article titles, which narrowed the search to 326 (114 Pubmed, 192 Embase, 20 CINAHL). Articles were not limited by date. Literature reviews that were not systematic, publications that were not peer-reviewed, and descriptive case reports were excluded. Duplicate articles were removed. Treatments directed to non-spinal cord etiologies or those that did not differentiate among location (spinal cord vs. supraspinal vs. peripheral) and/or types (neuropathic versus nociceptive) of pain were also excluded, and clinical judgment was exercised when interpretable based on description and location of the

pain, in an effort to be inclusive when appropriate. Articles were included only if QoL was considered as an outcome (primary or secondary) following an intervention for CNP treatment, leaving 153 abstracts/articles for analysis in this review.

Results

Twenty-one interventional studies met inclusion criteria and were reviewed (see Figure 1). Across all studies, 910 patients were analyzed (438 SCI, 290 MS, 182 other). There were no studies focused on patients with NMOSD.

Sex was described in all but one study (*n*=24). Of the remaining aggregate sample of 886, 53% of participants were female. Demographic characteristics of race/ethnicity were described only in the three U.S. studies (aggregate *n*=263). Among these, 236 were White/Caucasian descent (90%), 22 were Black/African descent (8%), three were Hispanic/Latino descent (1%), one was Native American and one was classified as "other."

Effect of Pharmacologic Interventions on QoL

Thirteen studies examined the effect of a pharmacologic intervention or treatment on QoL as a primary or secondary outcome (Table 2). Five studies evaluated the benefit of anti-epileptic medications (AEDs) for first-line treatment for CNP (Finnerup et al., 2015) in MS (2 studies), SCI (2 studies) and one was in a heterogeneous group of patients with CNP, a subset of whom had an undifferentiated spinal etiology. The rationale for using this class of medication for treatment of CNP was similar to the rationale for use in seizures: the drugs decrease hyperexcitability in damaged areas of the CNS caused by a sustained depolarization and inhibit voltage-dependent sodium channels, reducing the capacity of neurons to generate high-frequency action potentials (Salinas et al., 2012). A randomized, double-blind, placebo-

controlled clinical trial using early AED intervention with carbamazepine to prevent the onset of CNP in SCI did not show a significant difference between the intervention and control groups (Salinas et al., 2012) suggesting that preemptive analgesia does not prevent the subsequent onset of CNP. The other four studies were conducted using patients after CNP onset, three of which found that reducing pain positively impacted QoL. Gabapentin, pregabalin and levetiracetam reduced pain by 50-100% on average and improved self-reported Visual Acuity Scale ratings through the course of treatment (Levendoglu, Ogun, Ozerbil, Ogun & Ugurlu, 2004; Vranken et al., 2008; Rossi et al., 2009) (Table 2). Overall, these findings support that use of AEDs for CNP treatment and improvement of QoL.

Two RCTs studied the effects of the serotonin noradrenaline reuptake inhibitor (SNRI) duloxetine use on pain (Vranken et al., 2011; Vollmer, Robinson, Risser & Malcolm, 2014), although SNRIs are not as commonly used for pain worldwide compared to tricyclic anti-depressants (Finnerup et al., 2015). The stated rationale for using duloxetine was to inhibit the reuptake of serotonin and noradrenaline to potentiate monoamine neurotransmission in the descending inhibitory spinal pathways. This results in reduced nociceptive afferent transmission in the ascending spinal pain pathways to decrease the sensation of pain. Potentiation of both serotonin and noradrenaline is required to produce effective analgesia (Lunn, Hughes & Wiffen, 2014). The smaller of these studies (n=40) examined the effects of duloxetine in SCI-induced pain showed improvements in QoL including in the area of pain, but no improvement in independent pain scales (Vranken et al., 2011). In the larger study (n=239) duloxetine in MS patients with CNP resulted in significant reductions in pain throughout the end of the extension phase, without effecting any change in QoL (Vollmer et al, 2014). These seemingly conflicting results may be because the studies

used different survey tools, highlighting the importance of using standardized, validated measures of pain and quality of life.

Cannabinoid agents were investigated in two small RCTs, both in MS (Svendsen et al., 2004; Turcotte et al., 2015). Cannabinoids are ligands that bind on the presynaptic cannabinoid receptor, resulting in reduced calcium influx from voltage-gated calcium channels and hyperpolarization, thus decreasing cellular excitability (Turcotte et al., 2015). Both of the cannabinoid agents used in these studies uncovered a significant impact on pain with the larger of the two additionally impacting QoL. The smaller, more recent study evaluated the use of nabilone, a synthetic tetrahydrocannabinol, in patients who were already on stable doses of gabapentin (Turcotte et al., 2015). As used this study, multimodal approaches to CNP treatment that target dual mechanisms of CNP treatment may be more effective at improving both pain and QoL.

Two opioids were assessed for treatment of CNP: tramadol and oxycodone. Opioids bind to an opioid receptor, causing inhibition of adenylyl-cyclase and hyperpolarization of neurons, and decreased excitability (Ordonez Gallego, Gonzalez Baron & Espinosa Arranz, 2007). One of the medications, tramadol, has a second mechanism of action similar to SNRIs, as described above (Norrbrink and Lundeberg, 2009). Both studies showed improvement in pain, though a limitation of the oxycodone study (Ordonez Gallego et al., 2007) is that it was an observational study and oxycodone dosing was not standardized by the study protocol.

Another study examined the effect of botulinum toxin type A (BTX-A) for CNP treatment in patients with SCI (n=40). The mechanism of action proposed in CNP is based on its mechanism in nociceptive pain, which suggests that BTX-A may inhibit neurogenic

inflammation and the peripheral sensitization of nerve fibers by inhibiting the release of local neuropeptides, thereby reducing pain. The study reported a significant reduction in pain, though only a marginal trend toward significance on QoL.

Intravenous immunoglobulin (IVIG) contains the pooled polyvalent IgG antibodies extracted from the plasma of thousands of blood donors and is generally used to decrease inflammation. The exact mechanism of action has not been well-elucidated, but it is theorized that a high load of exogenous antibodies leads to a robust antibody recycling process that turns over both exogenous and endogenous antibodies (Sapir & Shoenfeld, 2005). This therapy was examined in post-polio syndrome (n=142; 75 with CNP): polio causes acute inflammation of the spinal cord leading to weakness, fatigue and pain persisting long after the acute infection has resolved (Gonzalez et al., 2006). Ongoing denervation has been suggested to be the most important reason for progressive muscle weakness associated with poliomyelitis infection. Patients with post-polio syndrome have increased expression of messenger RNA for proinflammatory cytokines in cerebrospinal fluid, which may suggest an ongoing inflammatory process in the CNS (Gonzalez et al., 2006). As such, the researchers hypothesized that targeting inflammation with IVIG may improve weakness or stop its progression. Pain was a secondary study outcome, but notably it was reduced in this patient population. QoL was not significantly impacted.

Effect of Non-pharmacologic Interventions on QoL

Eight studies were identified that examined the effect of a non-pharmacologic intervention for CNP on QoL. Non-pharmacologic interventions included the use of physical therapy (PT) and exercise, transcutaneous electrical nerve stimulation (TENS), cognitive

behavioral therapy (CBT) and complementary and alternative medicine (CAM) approaches (Table 3).

In rats, regular moderate aerobic exercise reversed signs of CNP and increased endogenous opioid content in brainstem regions important in pain modulation (Stagg et al., 2011). This approach was translated to a small human study in SCI that showed significant improvements in both QoL and pain, suggesting that a larger study with PT and exercise is warranted (Norrbrink, Lindberg, Wahman, & Bjerkefors, 2012). Transcutaneous electrical nerve stimulation (TENS) uses electric current to stimulate denervated nerves through electrodes placed on the skin (Norrbrink, 2009). Effectiveness has been shown for use in peripheral neuropathy, but results in the treatment of central NP have been equivocal. Sites in the spinal cord and brainstem that utilize opioid, serotonin, and muscarinic receptors have been shown to be activated by peripheral nerve stimulation by TENS, but lack of standards on ideal frequency and stimulation amplitude needed to achieve pain reduction has hampered the use of TENS in clinical trials of CNP (Norrbrink, 2009; Sluka et al., 2013).

Psychological factors are believed to influence the maintenance and aggravation of CNP, suggesting that psychological interventions with traditional biomedical interventions may reduce the burden of CNP (Heutink et al., 2014). Four studies evaluated the effectiveness of Cognitive Behavioral Therapy (CBT) for CNP treatment, all in SCI (Norrbrink Budh, Kowalski, & Lundeberg, 2006; Nicholson Perry et al., 2009; Heutink et al., 2012; Heutink et al., 2014). CBT focuses on modifying an individual's beliefs, expectations and coping abilities (Norrbrink Budh et al., 2006). One study reduced pain without improving QoL, two studies improved QoL only, and one had no impact on pain or QoL. CBT is aimed at modifying a patient's *response* to pain rather than directed at the pain itself, explaining the

finding that three of the studies did not impact pain significantly. Interestingly, all four studies had some impact on anxiety and/or depression, adding strength to the argument that this intervention improves pain responses rather than the physical experience of pain itself.

Complementary and Alternative Medicine (CAM) refers to treatments that are outside of conventional medicine which have for the most part not been rigorously tested and often evolve from traditional Asian medicine. The American public's use of CAM therapeutic modalities has grown exponentially in recent years, including for CNP (Namjooyan et al., 2014). This may be a product of the fact that CNP is often not affected in a clinically meaningful way, leading patients to look for other options. Common examples of these are acupuncture and massage therapy. Acupuncture is the stimulation of specific points through which the life-energy flows along the skin of the body using thin needles, in an attempt to achieve balance. Healing Touch (HT) similarly aims to achieve balance in life-energy through touch. Progressive muscle relaxation (PMR) is a technique focused on controlling the state of muscular tension and involves learning to monitor tension in each specific muscle group in the body by deliberately inducing and releasing tension in each group. The study examining HT versus PMR was the only mixed methods study reviewed; no significant impact was found on pain and QoL differences favoring HT were captured in the qualitative component alone (Wardell, Rintala, Duan, & Tan, 2006). In the study investigating the effects of acupuncture versus massage therapy, no differences in amount of pain were found but the data suggest that acupuncture may have prevented worsening of pain compared to therapeutic massage (Norrbrink and Lundeberg, 2011).

The concept of integrative medicine combines evidence-based treatments with alternative and non-pharmacologic options, in an attempt to approach treatment in a more

holistic manner, and may be a promising next step in this arena. There are no trials or studies that systematically used a combination of pharmacologic and non-pharmacologic treatments for central spinal CNP using QoL as an outcome measure.

Discussion

This is a comprehensive literature review examining the state of the science in spinal CNP treatment utilizing QoL as a primary or secondary measure. Hundreds of articles were found that examined the impact of a given intervention on CNP or the impact of CNP on QoL, but only these 21 could be identified that included an examination of the impact of a pain intervention on QoL. However, impacting pain alone may not be clinically meaningful to a patient if QoL is not also enhanced. Given that pain affects QoL (Newland et al., 2009; Kanamori, 2011), it seems reasonable that an objective of pain treatment should be aimed at improving QoL in patients as well. It is striking that so few studies have applied QoL measures as an outcome. In order to meet patient-centered goals of improving QoL, future studies should include measures of both pain and QoL.

Also notable is the seeming mismatch between reported effects on pain levels and QoL, such that improvement in pain did not necessarily translate to improvement in QoL: of the 21 studies examined, 6 were shown to positively impact both pain and QoL, 4 failed to impact either, 7 impacted pain only and 4 impacted QoL only. There are several possible explanations as to why half of the studies had a mismatch between effects on pain and effects on QoL. First, many of the studies were relatively small, with a median sample size of 29.5 (range 8-239). Thus, some studies may have been adequately powered to address the primary outcome, but not sufficiently powered to identify significant differences in secondary

outcomes, including QoL. Second, there was a wide array of both pain measures and QoL measures used, and while most have been validated in some populations, not all have been validated specifically in the populations that were investigated; see reviews of instruments for SCI, MS, and NP (Breivik et al., 2008; Stadhouder et al., 2010; Kuspinar and Mayo, 2014). Using validated measurement tools, or combining tools may draw out significant findings.

Another possible explanation for the mismatch between treatment of NP and its effect on QoL could be explained by recent research on symptom clusters. Symptom clusters consist of two or more related symptoms that co-occur and that may or may or may not share a common etiology (Kim, Abraham, & Malone, 2013). In chronic disorders, patients often present with multiple inter-related symptoms, which may explain why treating one symptom does not necessarily impact quality of life. While much of the research in symptom clusters has focused on cancer, the concept is applicable to a wide array of chronic conditions, including NMOSD, MS and SCI. The implication for NMOSD is that treating CNP in isolation may not impact QoL in a disease that causes other debilitating symptoms, including anxiety, depression, fatigue, sleep dysfunction and bladder dysfunction (Pan et al., 2015; Mutch et al., 2015; Hollinger et al., 2016; Shi et al., 2016; Mealy, Boscoe, Caro & Levy, M. 2018).

There was relative balance in the number of females to males represented overall (54%). SCI made up 39% of the total number of participants among trials, which has a high male-to-female ratio of 2.6-7:1 internationally (Singh, Tetreault, Kalsi-Ryan, Nouri & Fehlings, 2014). Counterbalancing this were the MS patients (42% of the total sample) where the female-to-male ratio is 2-3:1 (Koch-Henriksen & Sørensen, 2010). Only three studies reported on race/ethnicity, and all of these were from the United States and all predominantly

white. Although many of the countries represented are fairly homogenous groups, demographics continue to change worldwide and it is problematic to fail to report on social determinants of health and inequities between groups, especially among groups where health inequities are known to be present and where perceptions of pain differ (Bernardes, Keogh & Lima, 2008; Rahim-Williams et al., 2012). Some research suggests that biopsychosocial mechanisms may underlie these differences (Paller, Campbell, Edwards, & Dobs, 2009). Of interest would be a comparison of responses to non-pharmacologic interventions, and particularly to CBT which is guided by the biopsychosocial model (Nicholson Perry et al., 2009; Heutink et al., 2012; Heutink et al., 2014).

Conclusion

NMOSD causes damage to CNS pathways in the spinal cord as occurs in MS and SCI, suggesting that it is reasonable to extrapolate data from MS and SCI to guide therapy in NMOSD while also recognizing that different outcomes may result in part due to disparities in sex and race in NMOSD. CNP is difficult to treat and is pervasive in NMOSD. Treatments are ineffective and individual pain interventions are not sufficient to impact QoL. These factors only further underscore the need for broadening treatment options and using a multimodal approach in this population. It is important to focus attention on what symptoms form clusters and on comprehensive treatment regimens that address these clusters. A practical and potentially clinically meaningful trial for future research may examine a combination of an AED, anti-depressant, CBT and exercise program. This may highlight how the cluster of symptoms is impacted differently between the two groups, with emphasis on how this translates to improved quality of life.

References

Araki, M., Matsuoka, T., Miyamoto, K., Kusunoki, S., Okamoto, T., Murata, M., . . . Yamamura, T. (2014). Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: A pilot study.*Neurology, 82*(15), 1302-1306. doi:10.1212/WNL.0000000000000317 [doi]

Asseyer, S., Schmidt, F., Chien, C., Scheel, M., Ruprecht, K., Bellmann-Strobl, J., . . . Paul, F. (2018). Pain in AQP4-IgG-positive and MOG-IgG-positive neuromyelitis optica spectrum disorders. *Multiple Sclerosis Journal - Experimental, Translational and Clinical, 4*(3), 2055217318796684. doi:10.1177/2055217318796684 [doi]

Bernardes, S. F., Keogh, E., & Lima, M. L. (2008). Bridging the gap between pain and gender research: A selective literature review. *European Journal of Pain (London, England), 12*(4), 427-440. doi:S1090-3801(07)00646-5 [pii]

Boldt, I., Eriks-Hoogland, I., Brinkhof, M. W., de Bie, R., Joggi, D., & von Elm, E. (2014). Non-pharmacological interventions for chronic pain in people with spinal cord injury. *The Cochrane Database of Systematic Reviews, 11*, CD009177. doi:10.1002/14651858.CD009177.pub2 [doi]

Borsook, D. (2012). Neurological diseases and pain. *Brain : A Journal of Neurology, 135*(Pt 2), 320-344. doi:10.1093/brain/awr271 [doi]

Bradl, M., Kanamori, Y., Nakashima, I., Misu, T., Fujihara, K., Lassmann, H., & Sandkuhler, J. (2014). Pain in neuromyelitis optica--prevalence, pathogenesis and therapy. *Nature Reviews.Neurology, 10*(9), 529-536. doi:10.1038/nrneurol.2014.129 [doi]

Breivik, H., Borchgrevink, P. C., Allen, S. M., Rosseland, L. A., Romundstad, L., Hals, E. K., . . . Stubhaug, A. (2008). Assessment of pain. *British Journal of Anaesthesia, 101*(1), 17-24. doi:10.1093/bja/aen103 [doi]

Breuer, B., Pappagallo, M., Knotkova, H., Guleyupoglu, N., Wallenstein, S., & Portenoy, R. K. (2007). A randomized, double-blind, placebo-controlled, two-period, crossover, pilot trial of lamotrigine in patients with central pain due to multiple sclerosis. *Clinical Therapeutics, 29*(9), 2022-2030. doi:S0149-2918(07)00304-9 [pii]

Centonze, D. (2014). Advances in the management of multiple sclerosis spasticity: Multiple sclerosis spasticity nervous pathways. *European Neurology, 72 Suppl 1*, 6-8. doi:10.1159/000367615 [doi]

Eaneff, S., Wang, V., Hanger, M., Levy, M., Mealy, M. A., Brandt, A. U., . . . Wicks, P. (2017). Patient perspectives on neuromyelitis optica spectrum disorders: Data from the PatientsLikeMe online community. *Multiple Sclerosis and Related Disorders, 17*, 116-122. doi:S2211-0348(17)30164-5 [pii]

Finnerup, N. B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R. H., . . . Wallace, M. (2015). Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *The Lancet.Neurology, 14*(2), 162-173. doi:10.1016/S1474-4422(14)70251-0 [doi]

Gonzalez, H., Sunnerhagen, K. S., Sjoberg, I., Kaponides, G., Olsson, T., & Borg, K. (2006). Intravenous immunoglobulin for post-polio syndrome: A randomised controlled trial. *The Lancet.Neurology, 5*(6), 493-500. doi:S1474-4422(06)70447-1 [pii]

Han, Z. A., Song, D. H., Oh, H. M., & Chung, M. E. (2016). Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. *Annals of Neurology, 79*(4), 569-578. doi:10.1002/ana.24605 [doi]

Heutink, M., Post, M. W., Bongers-Janssen, H. M., Dijkstra, C. A., Snoek, G. J., Spijkerman, D. C., & Lindeman, E. (2012). The CONECSI trial: Results of a randomized controlled trial of a multidisciplinary cognitive behavioral program for coping with chronic neuropathic pain after spinal cord injury. *Pain, 153*(1), 120-128. doi:10.1016/j.pain.2011.09.029 [doi]

Heutink, M., Post, M. W., Luthart, P., Schuitemaker, M., Slangen, S., Sweers, J., . . . Lindeman, E. (2014). Long-term outcomes of a multidisciplinary cognitive behavioural programme for coping with chronic neuropathic spinal cord injury pain. *Journal of Rehabilitation Medicine, 46*(6), 540-545. doi:10.2340/16501977-1798 [doi]

Hollinger, K. R., Franke, C., Arenivas, A., Woods, S. R., Mealy, M. A., Levy, M., & Kaplin, A. I. (2016). Cognition, mood, and purpose in life in neuromyelitis optica spectrum disorder. *Journal of the Neurological Sciences, 362*, 85-90. doi:10.1016/j.jns.2016.01.010 [doi]

Huang, Q., Wang, J., Zhou, Y., Yang, H., Wang, Z., Yan, Z., . . . Qiu, W. (2018). Low-dose mycophenolate mofetil for treatment of neuromyelitis optica spectrum disorders: A

prospective multicenter study in south china. *Frontiers in Immunology, 9*, 2066. doi:10.3389/fimmu.2018.02066 [doi]

Jarius, S., Ruprecht, K., Wildemann, B., Kuempfel, T., Ringelstein, M., Geis, C., . . . Paul, F. (2012). Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients. *Journal of Neuroinflammation, 9*, 14-2094-9-14. doi:10.1186/1742-2094-9-14 [doi]

Kanamori, Y., Nakashima, I., Takai, Y., Nishiyama, S., Kuroda, H., Takahashi, T., . . . Itoyama, Y. (2011). Pain in neuromyelitis optica and its effect on quality of life: A cross-sectional study. *Neurology, 77*(7), 652-658. doi:10.1212/WNL.0b013e318229e694 [doi]

Kim, H. J., Abraham, I., & Malone, P. S. (2013). Analytical methods and issues for symptom cluster research in oncology. *Current Opinion in Supportive and Palliative Care, 7*(1), 45-53. doi:10.1097/SPC.0b013e32835bf28b [doi]

Koch-Henriksen, N., & Sørensen, P. S. (2010). The changing demographic pattern of multiple sclerosis epidemiology. *The Lancet Neurology, 9*(5), 520-532. doi:http://dx.doi.org/10.1016/S1474-4422(10)70064-8

Kuspinar, A., & Mayo, N. E. (2014). A review of the psychometric properties of generic utility measures in multiple sclerosis. *Pharmacoeconomics, 32*(8), 759-773. doi:10.1007/s40273-014-0167-5 [doi]

Levendoglu, F., Ogun, C. O., Ozerbil, O., Ogun, T. C., & Ugurlu, H. (2004). Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine, 29*(7), 743-751. doi:00007632-200404010-00007 [pii]

Lunn, M. P., Hughes, R. A., & Wiffen, P. J. (2014). Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *The Cochrane Database of Systematic Reviews, 1*, CD007115. doi:10.1002/14651858.CD007115.pub3 [doi]

Marrie, R. A., & Gryba, C. (2013). The incidence and prevalence of neuromyelitis optica: A systematic review. International Journal of MS Care, 15(3), 113-118. doi:10.7224/1537-2073.2012-048 [doi]

Mealy, M. A., Kessler, R. A., Rimler, Z., Reid, A., Totonis, L., Cutter, G., . . . Levy, M. (2018). Mortality in neuromyelitis optica is strongly associated with african ancestry. *Neurology(R) Neuroimmunology & Neuroinflammation, 5*(4), e468. doi:10.1212/NXI.0000000000000468 [doi]

Mealy, M. A., Boscoe, A., Caro, J., Levy, M. (2018). Assessment of Patients with Neuromyelitis Optica Spectrum Disorder Using EQ-5D. *Int J MS Care.* Online ahead of print: doi.org/10.7224/1537-2073.2017-076.

Mealy, M. A., Wingerchuk, D. M., Greenberg, B. M., & Levy, M. (2012). Epidemiology of neuromyelitis optica in the united states: A multicenter analysis. *Archives of Neurology, 69*(9), 1176-1180. doi:10.1001/archneurol.2012.314 [doi]

Mutch, K., Methley, A., Moore, P., & Jacob, A. (2014). Life on hold: The experience of living with neuromyelitis optica. *Disability and Rehabilitation, 36*(13), 1100-1107. doi:10.3109/09638288.2013.833301 [doi]

Mutch, K., Zhao, S., Hamid, S., Methley, A., Elsone, L., Singh, G., . . . Jacob, A. (2015). Bladder and bowel dysfunction affect quality of life. A cross sectional study of 60 patients with aquaporin-4 antibody positive neuromyelitis optica spectrum disorder. *Multiple Sclerosis and Related Disorders, 4*(6), 614-618. doi:10.1016/j.msard.2015.07.015 [doi]

Namjooyan, F., Ghanavati, R., Majdinasab, N., Jokari, S., & Janbozorgi, M. (2014). Uses of complementary and alternative medicine in multiple sclerosis. *Journal of Traditional and Complementary Medicine, 4*(3), 145-152. doi:10.4103/2225-4110.136543 [doi]

Newland, P. K., Naismith, R. T., & Ullione, M. (2009). The impact of pain and other symptoms on quality of life in women with relapsing-remitting multiple sclerosis. *The Journal of Neuroscience Nursing : Journal of the American Association of Neuroscience Nurses, 41*(6), 322-328.

Nicholson Perry, K., Nicholas, M. K., Middleton, J., & Siddall, P. (2009). Psychological characteristics of people with spinal cord injury-related persisting pain referred to a tertiary pain management center.*Journal of Rehabilitation Research and Development, 46*(1), 57-67.

Norrbrink Budh, C., Kowalski, J., & Lundeberg, T. (2006). A comprehensive pain management programme comprising educational, cognitive and behavioural

interventions for neuropathic pain following spinal cord injury. *Journal of Rehabilitation Medicine, 38*(3), 172-180. doi:M1N46588657H1718 [pii]

Norrbrink, C. (2009). Transcutaneous electrical nerve stimulation for treatment of spinal cord injury neuropathic pain. *Journal of Rehabilitation Research and Development, 46*(1), 85-93.

Norrbrink, C., Lindberg, T., Wahman, K., & Bjerkefors, A. (2012). Effects of an exercise programme on musculoskeletal and neuropathic pain after spinal cord injury--results from a seated double-poling ergometer study. *Spinal Cord, 50*(6), 457-461. doi:10.1038/sc.2011.160 [doi]

Norrbrink, C., & Lundeberg, T. (2009). Tramadol in neuropathic pain after spinal cord injury: A randomized, double-blind, placebo-controlled trial. *The Clinical Journal of Pain, 25*(3), 177-184. doi:10.1097/AJP.0b013e31818a744d [doi]

Norrbrink, C., & Lundeberg, T. (2011). Acupuncture and massage therapy for neuropathic pain following spinal cord injury: An exploratory study. *Acupuncture in Medicine : Journal of the British Medical Acupuncture Society, 29*(2), 108-115. doi:10.1136/aim.2010.003269 [doi]

Ordonez Gallego, A., Gonzalez Baron, M., & Espinosa Arranz, E. (2007). Oxycodone: A pharmacological and clinical review. *Clinical & Translational Oncology : Official Publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico, 9*(5), 298-307. doi:946 [pii]

Paller, C. J., Campbell, C. M., Edwards, R. R., & Dobs, A. S. (2009). Sex-based differences in pain perception and treatment. *Pain Medicine (Malden, Mass.), 10*(2), 289-299. doi:10.1111/j.1526-4637.2008.00558.x [doi]

Pan, J., Zhao, P., Cai, H., Su, L., Wood, K., Shi, F. D., & Fu, Y. (2015). Hypoxemia, sleep disturbances, and depression correlated with fatigue in neuromyelitis optica spectrum disorder. *CNS Neuroscience & Therapeutics, 21*(7), 599-606. doi:10.1111/cns.12411 [doi]

Pellkofer, H. L., Havla, J., Hauer, D., Schelling, G., Azad, S. C., Kuempfel, T., . . . Huge, V. (2013). The major brain endocannabinoid 2-AG controls neuropathic pain and mechanical hyperalgesia in patients with neuromyelitis optica. *PloS One, 8*(8), e71500. doi:10.1371/journal.pone.0071500 [doi]

Popescu, B. F., & Lucchinetti, C. F. (2016). Immunopathology: Autoimmune glial diseases and differentiation from multiple sclerosis. *Handbook of Clinical Neurology, 133*, 95-106. doi:10.1016/B978-0-444-63432-0.00006-2 [doi]

Qian, P., Lancia, S., Alvarez, E., Klawiter, E. C., Cross, A. H., & Naismith, R. T. (2012). Association of neuromyelitis optica with severe and intractable pain. *Archives of Neurology, 69*(11), 1482-1487. doi:1355367 [pii]

Rahim-Williams, B., Riley, J. L.,3rd, Williams, A. K., & Fillingim, R. B. (2012). A quantitative review of ethnic group differences in experimental pain response: Do biology, psychology, and culture matter?*Pain Medicine (Malden, Mass.), 13*(4), 522-540. doi:10.1111/j.1526-4637.2012.01336.x [doi]

Ringelstein, M., Ayzenberg, I., Harmel, J., Lauenstein, A. S., Lensch, E., Stogbauer, F., . . . Kleiter, I. (2015). Long-term therapy with interleukin 6 receptor blockade in highly active neuromyelitis optica spectrum disorder. *JAMA Neurology, 72*(7), 756-763. doi:10.1001/jamaneurol.2015.0533 [doi]

Rossi, S., Mataluni, G., Codeca, C., Fiore, S., Buttari, F., Musella, A., . . . Centonze, D. (2009). Effects of levetiracetam on chronic pain in multiple sclerosis: Results of a pilot, randomized, placebo-controlled study. *European Journal of Neurology, 16*(3), 360-366. doi:10.1111/j.1468-1331.2008.02496.x [doi]

Salinas, F. A., Lugo, L. H., & Garcia, H. I. (2012). Efficacy of early treatment with carbamazepine in prevention of neuropathic pain in patients with spinal cord injury. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists, 91*(12), 1020-1027. doi:10.1097/PHM.0b013e3182643c85 [doi]

Sapir, T., & Shoenfeld, Y. (2005). Facing the enigma of immunomodulatory effects of intravenous immunoglobulin. *Clinical Reviews in Allergy & Immunology, 29*(3), 185-199. doi:CRIAI:29:3:185 [pii]

Shi, Z., Chen, H., Lian, Z., Liu, J., Feng, H., & Zhou, H. (2016). Factors that impact health-related quality of life in neuromyelitis optica spectrum disorder: Anxiety, disability, fatigue and depression. *Journal of Neuroimmunology, 293*, 54-58. doi:10.1016/j.jneuroim.2016.02.011 [doi]

Singh, A., Tetreault, L., Kalsi-Ryan, S., Nouri, A., & Fehlings, M. G. (2014). Global prevalence and incidence of traumatic spinal cord injury. *Clinical Epidemiology, 6*, 309-331. doi:10.2147/CLEP.S68889 [doi]

Sjolund, B. H. (2002). Pain and rehabilitation after spinal cord injury: The case of sensory spasticity? *Brain Research.Brain Research Reviews, 40*(1-3), 250-256. doi:S0165017302002072 [pii]

Sluka, K. A., Bjordal, J. M., Marchand, S., & Rakel, B. A. (2013). What makes transcutaneous electrical nerve stimulation work? making sense of the mixed results in the clinical literature. *Physical Therapy, 93*(10), 1397-1402. doi:10.2522/ptj.20120281 [doi]

Stadhouder, A., Buckens, C. F., Holtslag, H. R., & Oner, F. C. (2010). Are existing outcome instruments suitable for assessment of spinal trauma patients? *Journal of Neurosurgery.Spine, 13*(5), 638-647. doi:10.3171/2010.5.SPINE09128 [doi]

Stagg, N. J., Mata, H. P., Ibrahim, M. M., Henriksen, E. J., Porreca, F., Vanderah, T. W., & Philip Malan, T.,Jr. (2011). Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. *Anesthesiology, 114*(4), 940-948. doi:10.1097/ALN.0b013e318210f880 [doi]

Svendsen, K. B., Jensen, T. S., & Bach, F. W. (2004). Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? randomised double blind placebo controlled crossover trial. *BMJ (Clinical Research Ed.), 329*(7460), 253. doi:10.1136/bmj.38149.566979.AE [doi]

Todd, A. J. (2010). Neuronal circuitry for pain processing in the dorsal horn. *Nature Reviews.Neuroscience, 11*(12), 823-836. doi:10.1038/nrn2947 [doi]

Turcotte, D., Doupe, M., Torabi, M., Gomori, A., Ethans, K., Esfahani, F., . . . Namaka, M. (2015). Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: A randomized controlled trial. *Pain Medicine (Malden, Mass.), 16*(1), 149-159. doi:10.1111/pme.12569 [doi]

Vollmer, T. L., Robinson, M. J., Risser, R. C., & Malcolm, S. K. (2014). A randomized, double-blind, placebo-controlled trial of duloxetine for the treatment of pain in patients with multiple sclerosis. *Pain Practice : The Official Journal of World Institute of Pain, 14*(8), 732-744. doi:10.1111/papr.12127 [doi]

Vranken, J. H., Dijkgraaf, M. G., Kruis, M. R., van der Vegt, M. H., Hollmann, M. W., & Heesen, M. (2008). Pregabalin in patients with central neuropathic pain: A randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain, 136*(1-2), 150-157. doi:S0304-3959(07)00369-7 [pii]

Vranken, J. H., Hollmann, M. W., van der Vegt, M. H., Kruis, M. R., Heesen, M., Vos, K., . . . Dijkgraaf, M. G. (2011). Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: A randomized, double-blind, placebo-controlled trial. *Pain, 152*(2), 267-273. doi:10.1016/j.pain.2010.09.005 [doi]

Wardell, D. W., Rintala, D. H., Duan, Z., & Tan, G. (2006). A pilot study of healing touch and progressive relaxation for chronic neuropathic pain in persons with spinal cord

injury. *Journal of Holistic Nursing : Official Journal of the American Holistic Nurses' Association, 24*(4), 231-40; discussion 241-4. doi:24/4/231 [pii]

Widerstrom-Noga, E. G., & Turk, D. C. (2003). Types and effectiveness of treatments used by people with chronic pain associated with spinal cord injuries: Influence of pain and psychosocial characteristics.*Spinal Cord, 41*(11), 600-609. doi:10.1038/sj.sc.3101511 [doi]

Wingerchuk, D. M., Hogancamp, W. F., O'Brien, P. C., & Weinshenker, B. G. (1999). The clinical course of neuromyelitis optica (devic's syndrome). *Neurology, 53*(5), 1107-1114.

Wingerchuk, D. M., Lennon, V. A., Pittock, S. J., Lucchinetti, C. F., & Weinshenker, B. G. (2006). Revised diagnostic criteria for neuromyelitis optica. *Neurology, 66*(10), 1485-1489. doi:66/10/1485 [pii]

Zhao, S., Mutch, K., Elsone, L., Nurmikko, T., & Jacob, A. (2014). Neuropathic pain in neuromyelitis optica affects activities of daily living and quality of life. *Multiple Sclerosis (Houndmills, Basingstoke, England), 20*(12), 1658-1661. doi:10.1177/1352458514522103 [doi]

Figure 1: Flowchart depicting study selection procedure

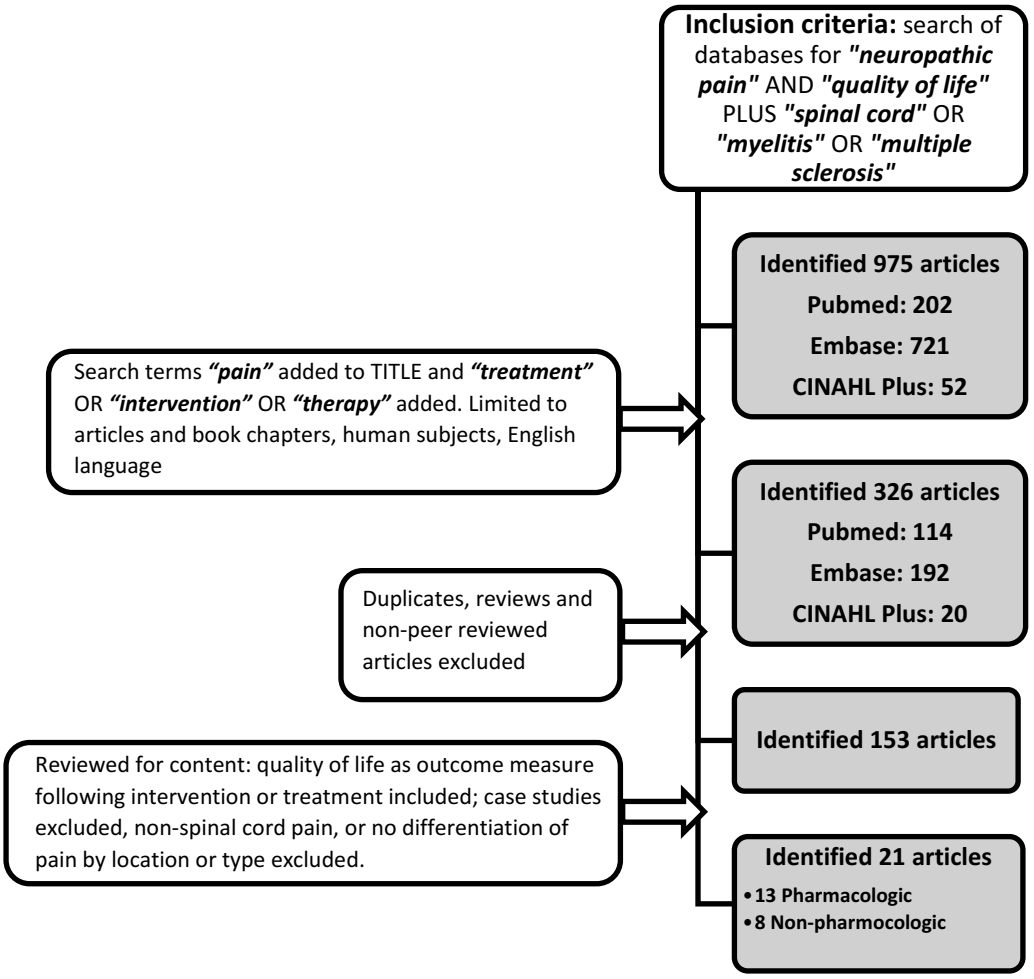


Table 1: Studies evaluating pain in NMOSD patients (listed chronologically)

Author (Year); Country	Patient Sample	Study Design	Pain Measure	QoL Measure	Findings & Comments*
Anti-Epileptics					
Kanamori et al. (2011); Japan	37 NMOSD patients (35 AQP4+; 36 female); 51 MS patients as comparator (37 female)	Descriptive comparative	BPI	SF-36	This was the first study that explored pain in NMO. Pain in NMOSD (83.8%) was more common than in MS (47.1%), and also more severe. QoL was also significantly poorer in the NMOSD group in the areas of bodily pain, physical functioning and general health. Consecutive sampling was used for participant recruitment. While this study did not investigate or account for medication use and was limited in the number of variables assessed, this pivotal study shed light on the issue of pain in NMO.
Qian et al. (2012); US	29 NMOSD patients (24 AQP4+; 24 female; 14 White/Caucasian, 14 Black/African descent, 1 Asian descent); 66 MS patients as comparator (52 female; 56 White/Caucasian, 10 Black/African descent)	Descriptive comparative	MPQ; 10-point NRS	SF-36	This study assessed pain and other symptoms, neurological function, spinal cord damage, and QoL. Pain in NMOSD (86.2%) was more common than in MS (40.9%), and also more severe, even after controlling for disability and spinal cord damage. Pain correlated with worse physical and mental scores on SF-36. This was the first study to examine medication use: prescription pain medications were used significantly more frequently in NMOSD participants, more often required multiple medications and all treated patients experienced pain despite treatment.
Pellkofer et al. (2013); Germany	11 NMOSD patients (11 AQP4+; 9 female; all White/Caucasian)	Descriptive	10-point NRS	SF-36	This study aimed to investigate presence and clinical characteristics of pain, stress and depression, and evaluated endocannabinoid levels and abnormalities in

					somatosensory functioning. Recruitment was through consecutive sampling. 91% endorsed NP within previous 3 months and 72% reported ongoing NP; decreased QoL in 3 of 8 measures: physical functioning, general health and bodily pain. This study also aimed to explore the role of endogenous cannabinoids and found plasma levels of 2-AG to be significantly higher in NMOSD patients, suggesting that central sensitization is controlled by it.
Zhao et al. (2014); UK	50 NMOSD patients (41 AQP4+; 39 female; no race/ethnicity data made available)	Descriptive	BPI	SF-36	This study specifically explored NP more in-depth. Patients were assessed for pain and QoL through use of structured interviews and measurement tools, and a retrospective record review was conducted to examine MRI data, medication use and neurologic functioning. 62% of patients experienced NP, with 68% of those having constant pain affecting ADLs. Interestingly, 72% of females versus 27% of males reported pain. 25% of patients reported pain as their worst symptom, despite mobility and/or vision issues. Physical component of QoL was equally low in those patients with and without pain, specifically in the areas of physical functioning, general health and bodily pain. Mental component was significantly lower in those with pain.
Mutch et al. (2014); UK	15 NMOSD patients (9 AQP4+; 11 female; no race/ethnicity data made available)	Qualitative descriptive	Semi-structured interviews	Semi-structured interviews	First qualitative study to explore QoL, including pain. Poor vision, reduced mobility, bladder dysfunction and pain affected participants' independence and experience of living with NMO. Expressed anxiety regarding unpredictability of disease and desire for normalcy.

					Patients reported anxiety and low mood, particularly following diagnosis and after relapses. Twelve patients reported pain, and indicated that it considerably affected their daily activities, mood, walking ability, enjoyment of life and relationships.
Asseyer et al. (2018); Germany	49 NMOSD patients (29 AQP4+, 14 MOG+; 41 female; no race/ethnicity data made available)	Descriptive	painDETECT	SF-36	Eighty-six percent of patients reported pain, regardless of antibody status. Pain correlated with QoL, but treatment of pain was not effective at improving QoL.
Eaneff et al. (2017); US, UK, Sweden	522 NMOSD patients (self-reported; AQP4 status unknown; 283 female; race data available for 142 patients: 99 White/Caucasian, 22 Black/African descent, 15 Asian; 6 other)	Descriptive	Self-report	PLM quality of life survey	This study reports the patient perspective of those with NMOSD via an online community called PatientsLikeMe and found that 53% of NMOSD patients report moderate to severe pain. Fifty-nine percent reported that their health limited their work and activities all or most of the time. Physical and emotional health interfered with social activities.

*values were considered significant at $p \leq 0.05$, unless otherwise noted

NMOSD=neuromyelitis optica spectrum disorder; MS=multiple sclerosis; NP=neuropathic pain; BPI=Brief Pain Inventory; SF-36=Short Form 36 health survey; AQP4+=aquaporin 4+; MPQ=McGill Pain Questionnaire; NRS=numeric rating scale; QoL=quality of life; 2-AG=2-Arachidonoylglycerol; ADLs=activities of daily living; PLM=PatientsLikeMe

Table 2: Trials examining the effect of pharmacologic interventions on QoL (grouped by mechanism)

Author (Year); Country	Patient Sample	Study Design	Intervention	QoL Measure	Findings & Comments*
Anti-Epileptics					
Levendoglu et al. (2004); Turkey	SCI patients c/ NP; *n*=20 (7 female; no race data made available)	RCT c/ cross-over	Gabapentin, titrated up to 3600 mg/day	Modified Lattinen Test	Significant decrease in intensity and frequency of most descriptors of pain (sharp, hot, unpleasant, deep, and surface) and disability and sleep were significantly better in the GBP treatment group. This was the 1st RCT to include QoL measures, in one of the most commonly used medications for NP treatment, however another measure of QoL would be helpful to capture a fuller picture of effects on health status.
Breuer et al. (2007); US	MS patients c/ spinal NP; *n*=12 (10 female; 8 white, 8 African descent)	RCT c/ cross-over	Lamotrigine in addition to stable regimen, titrated up to 400 mg	MSQoL-54	Pilot study showed no significant difference in pain or QoL; did not support need for larger trial.
Vranken et al. (2008); Netherlands	Patients c/ NP; subset was spinal; *n*=40 (19 female; 20 in treatment group; no race data made available); 21 patients with spinal cause	RCT	Pregabalin in addition to stable regimen, titrated up to 600 mg/day	EQ-5D; SF-36; PDI	There was significant decrease in mean pain score for pregabalin treatment group, compared with placebo. No difference in PDI between groups but treatment group showed significant improvement for the EQ-5D utility score and EQ-5D VAS score compared with the placebo group and SF-36 indicated that treatment led to a significant improvement in the bodily pain domain only.

Rossi et al. (2009); Italy	MS patients c/ spinal NP; *n*=20 (15 female; 12 in treatment group; no race data made available)	RCT	Levetiracetam, 500 mg/day	MSQoL-54	Significant reduction in pain for treatment group; no difference in reported QoL, except for the item, 'overall rating of quality of life.'
Salinas et al. (2012); Colombia	SCI patients s/ NP; *n*=46 (4 female; 24 in treatment group; no race data made available)	RCT	Carbamazepine, titrated up to 600 mg/day	SF-36	This novel study looked at prevention of NP with early treatment, rather than treatment in those who already experience it. Early intervention did not decrease incidence of NP over time and there was no difference in QoL between groups, despite appropriate power.
Anti-Depressants					
Vranken et al. (2011); Netherlands	SCI and stroke patients c/ NP; *n*=48 (24 in treatment group; Table 1, demographics, is missing from manuscript)	RCT	Duloxetine in addition to stable regimen, titrated up to 60 mg/day	EQ-5D; SF-36; PDI	No difference in pain intensity with treatment. Treatment group showed a significant improvement for the bodily pain domain only of the SF-36. No significant differences were observed in other QoL indices. The distribution of spinal versus supraspinal NP is said to be in Table 1 (Demographics), but no such table was included in the manuscript and spinal NP could not be separately assessed.
Vollmer et al. (2013); US	MS patients c/ spinal NP; *n*=239 (189 female; 221 white, 15 African descent, 2 Hispanic, 1 Native American; 118 in treatment group); 209 in OLE	Multi-center RCT, c/ OLE	Duloxetine in addition to stable regimen, titrated up to 60 mg/day in RCT and up to 120 mg/day in OLE	MSQoL-54	This well-conceived, well-executed, international study showed significant pain reduction in treatment group; QoL was not impacted. In OLE, pain reduction was reported in patients in both groups, with greater improvement reported by patients who had received placebo during the acute phase.
Cannabinoids					
Svendsen et al. (2004); Denmark	MS patients c/ spinal NP; *n*=24 (14 female; no race data made available)	RCT c/ cross-over	Dronabinol, titrated up to 10 mg	SF-36	Pain intensity and reduction significantly improved on treatment; the only improvements

					to QoL were seen in bodily pain and mental health.
Turcotte et al. (2015); Canada	MS patients c/ NP refractory to GPB; *n*=15 (13 female; 8 in treatment group; no race data made available)	RCT	Nabilone, titrated up to 1 mg, in addition to stable GBP dose	VAS_{impact}	This small but well-designed study explores the important need for combining medication therapies, and shows that combination of GBP with nabilone significantly reduces pain. No change in pain impact was noted, however, the use of a VAS to capture impact of pain may have been inadequate and a more comprehensive measure of QoL would have been prudent.
Opioids					
Norrbrink & Lundeberg (2009); Sweden	SCI patients c/ NP; *n*=35 (7 female; 23 in treatment group; no race data made available)	Multi-center RCT	Tramadol in addition to stable regimen, titrated up to 400 mg/day	LiSat-9	Decrease in pain intensity in treatment group compared with those on placebo. Global life satisfaction improved in placebo group only.
Barrera-Chacon et al. (2011); Spain	SCI patients c/ NP refractory to AED treatment; *n*=54 (10 female; no race data made available)	Multi-center, observational descriptive	Oxycodone, usually in conjunction with AED use	Modified EQ-5D	Significant decrease in pain intensity, improved health-related QoL and diminished impact of pain on physical activity and sleep. As doses of oxycodone were not investigated, further research in controlled trials assessing appropriate dosing for NP treatment is warranted.
Other					
Han et al. (2016); Korea	SCI patients c/ NP; n=40 (14 female; 20 in treatment group; no race data made available)	Multi-center RCT	BTX-A, 200 U subcutaneous injection, in addition to stable regimen	WHOQOL-BREF	The BTX-A group showed significant reductions in pain score at 4 and 8 weeks following injection, compared to placebo. Trend towards significant impact in physical health domain of QoL only.

Gonzalez et al. (2006); Sweden	Post-polio syndrome patients; subset had NP; *n*=142; 75 patients with NP (33 of whom are in treatment group; 92 females in total group, not differentiated by pain status; no race data made available)	RCT	IVIG, 90 g over 3 days c/ 2nd equal dose at 3 months	SF-36	Pain assessment was a secondary end-point of this study that primarily assessed strength, and not all patients included had NP. In the subcohort of patients with significant pain, those receiving IVIG had a greater pain reduction. QoL did not differ between groups.

*values were considered significant at $p \leq 0.05$, unless otherwise noted

SCI=spinal cord injury; MS=multiple sclerosis; NP=neuropathic pain; RCT=Randomized Controlled Trial; GBP=gabapentin; MSQoL=Multiple Sclerosis Quality of Life instrument; EQ-5D=EuroQoL-5 Dimensions instrument; VAS=Visual Analog Scale; WHOQOL-BREF=World Health Organization Quality of Life-abbreviated; PDI=Pain Disability Index; SF-36=Short Form 36 health survey; OLE=open-label extension; BTX-A= botulinum toxin type A; IVIG= Intravenous immunoglobulin

Table 3: Trials examining the effect of non-pharmacologic interventions on QoL (grouped by mechanism)

Author (Year); Country	Patient Sample	Study Design	Intervention	QoL Measure	Findings & Comments
Physical Medicine and Rehabilitation Medicine					
Norrbrink (2009); Sweden	SCI patients c/ NP; *n*=24 (4 female; no race data made available)	RCT c/ cross-over	Hi- versus low-frequency TENS	LiSat-9	In this study with high attrition and difficulty with enrollment, pain intensity was unchanged compared with baseline values on a group level and no differences were found between the two modes of stimulation, and no effect on secondary measures including life satisfaction was noted.
Norrbrink et al. (2012); Sweden	SCI patients c/ musculoskeletal and/or NP; *n*=8; 7 patients with NP pain (1 of whom is female; no race data made available)	Observational descriptive	10-week exercise program	SCI QoL data set	Descriptive statistics were utilized alone since inferences could not be made in this small cohort. For those with neuropathic pain, median pain intensity ratings decreased from 5 on a 0–10 numerical rating scale at baseline to 3 at the end of study. All median ratings of QoL showed improvement. Results in this exploratory study are promising and need to be further explored in a larger controlled study.
Cognitive Behavioral Therapy Programs					
Norrbrink Budh et al. (2006); Sweden	SCI patients c/ NP; *n*=38 (24 female; 27 in treatment group; no race data made available)	Quasi-experimental	CBT	NHP	In this non-randomized study, no difference from baseline in pain or QoL was found in treatment group, or between groups. Improvement in sleep quality and mood detected in treatment group, not affecting composite score.

Nicholson-Perry et al. (2009); Australia	SCI in patients c/ NP; n=36 (8 female; 19 in treatment group; no race data made available)	Quasi-experimental	CBT	Modified SF-36 with physical and mental domains	No changes in pain intensity between or within groups over time, though there was significant improvement in pain-catastrophizing for the treatment group. QoL improved for mental but not physical status.
Heutink et al. (2012); Netherlands	SCI patients c/ NP; *n*=61 (22 female; 31 in treatment group; no race data made available)	Multi-center unblinded RCT	CBT	LiSat-9	In the first RCT of CBT, short-term decrease in pain was detected, but this was not sustained at 3-month follow-up. No change in life satisfaction was identified, but anxiety and depression decreased in the intervention group.
Heutink et al. (2014); Netherlands	SCI patients c/ NP; *n*=29 (9 female; no race data made available)	Multi-center extension study of Heutink, 2012 (treatment group only)	CBT	LiSat-9	Pain intensity was significantly decreased at 12-month follow-up; no changes in life satisfaction or depression over time, though significant decrease in anxiety was noted.
Complementary and Alternative Medicine					
Wardell et al. (2006); US	SCI patients c/ NP; *n*=12 (0 female; 4 white, 3 African descent, 1 Hispanic, 1 other; 7 in HT group)	Quasi-experimental; Convergent Mixed Methods	Healing Touch (energy-based program) vs. Guided Progressive Relaxation	SWLS; unstructured focus groups & interviews, written responses	This small pilot study of all-male veterans did not reveal significant changes in pain or life satisfaction. However, the HT group had variable responses and the qualitative component indicated that a subset of patients experienced benefit suggesting that while this pilot study was not powered appropriately to find differences, a larger study may.
Norrbrink & Lundeberg (2011); Sweden	SCI patients c/ NP; *n*=30 (6 female; 15 in treatment group; no race data made available)	Quasi-experimental; Sequential Controlled-Trial	Acupuncture vs. Massage Therapy	LiSat-9	This small exploratory study found a significant difference between the two groups at end of treatment in favor of acupuncture, but no within-group differences in pain at follow-up. No impact on life satisfaction.

*values were considered significant at $p \leq 0.05$, unless otherwise noted

SCI=spinal cord injury; MS=multiple sclerosis; NP=neuropathic pain; RCT=Randomized Controlled Trial; GBP=gabapentin; SCI QoL=Spinal Cord Injury Quality of Life instrument; EQ-5D=EuroQoL-5 Dimensions instrument; HT=Healing Touch; SWLS=Satisfaction with Life Scale; LiSat-9=Life Satisfaction-9; CBT=Cognitive Behavioral Therapy: NHP=Nottingham Health Profile extension

Chapter 3: Scrambler therapy is a safe and feasible intervention that improves neuropathic pain in patients with neuromyelitis optica spectrum disorder: a phase II randomized controlled trial

(Manuscript 2)

Maureen A. Mealy, RN, PhD

Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Sharon L. Kozachik, PhD, RN

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Lawrence J. Cook, PhD

University of Utah, Department of Pediatrics, Salt Lake City, UT, USA

Lauren Totonis

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Ruth Andrea Salazar

Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA

Jerilyn K. Allen, PhD, RN

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Marie T. Nolan, PhD, RN

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Thomas J. Smith, MD

Johns Hopkins University School of Medicine, Department of Oncology, Baltimore, MD, USA

Michael Levy, MD, PhD

Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA

Abstract

The primary objective aimed to determine if Scrambler therapy is an effective, acceptable and feasible treatment of persistent central neuropathic pain in patients with neuromyelitis optica spectrum disorder (NMOSD). The secondary objective explored the effect of Scrambler therapy on co-occurring symptoms. We conducted a randomized single blind, sham-controlled trial in patients with NMOSD who have central neuropathic pain using Scrambler therapy for 10 consecutive weekdays. Pain severity, pain interference, anxiety, depression and sleep disturbance were assessed at baseline, end of treatment, and at 30- and 60-day follow-up. Twenty-two patients (11 per arm) were enrolled into and completed this trial. The median baseline NRS pain score decreased from 5.0 to 1.5 following 10 days of treatment with Scrambler therapy, whereas the median NRS score did not significantly decrease in the sham arm. Depression was also reduced in the treatment arm, and anxiety was decreased in a subset of patients who responded to treatment. These symptoms were not impacted in the sham arm. The safety profiles were similar between groups. Scrambler therapy is an effective, feasible and safe intervention for central neuropathic pain in patients with NMOSD. Decreasing pain with Scrambler therapy may additionally improve depression and anxiety.

Clinicaltrials.gov identifier

NCT03452176

Classification of Evidence

This study provides Class 1 evidence of Scrambler therapy use in patients diagnosed with NMOSD who have central neuropathic pain.

Scrambler therapy is a safe and feasible intervention that improves neuropathic pain in patients with neuromyelitis optica spectrum disorder: a phase II randomized controlled trial

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system that causes recurrent inflammatory attacks of the optic nerves and spinal cord, leading to blindness, paralysis and death (Oh & Levy, 2012). Despite these devastating consequences of the disease, patients have reported that pain is among the most prevalent and debilitating symptom which impacts mood, mobility and quality of life (QoL) (Qian et al., 2012; Zhao et al., 2014; Kanamori et al., 2011; Hollinger et al., 2016; Shi et al., 2016; Moore et al., 2016; Kong et al., 2016). In particular, central neuropathic pain is pervasive, severe, intractable to treatment, and affects 62-91% of patients with NMOSD (Zhao et al., 2014; Pellkofer et al, 2013). Currently, there is no standard of care for central neuropathic pain treatment, and the most frequently-used medications for its treatment in NMOSD are anti-epileptics, antidepressants and non-steroidal anti-inflammatory agents. Descriptive studies in NMOSD acknowledge the inadequate effect of these medications, and effective treatment for central neuropathic pain in NMOSD is still lacking (Qian et al., 2012; Zhao et al., 2014).

Scrambler therapy is a new, non-invasive technology with Food and Drug Administration (FDA) 510(k) approval, "Scrambler ST 5 TENS Device," (K081255) granted in February 2009 for acute, chronic and post-operative pain (FDA, 2019). Scrambler is a type of transcutaneous electrical nerve stimulation (TENS) that uses peripheral nerve stimulation of ascending C fibers to modify nociceptive responses with the intent of re-organizing maladaptive signaling pathways in the sensory cortex (Majithia et al., 2016). This neuromodulatory therapy has been investigated for treatment of persistent peripheral neuropathic pain, largely in open-label observational trials, in several conditions including chemotherapy-induced neuropathy, post-herpetic neuralgia and

post-surgical neuropathic pain with promising results (Majithia et al., 2016; Smith et al., 2017; Joo et al., 2017; Park et al., 2017; Kim et al., 2017; Kashyap et al., 2017; Smith et al., 2017). Patients report sustained relief after undergoing daily treatment sessions for 10 consecutive weekdays (Majithia et al., 2016).

There is anecdotal evidence supporting Scrambler therapy for use in patients with persistent central neuropathic pain (D'Amato et al., 2018; Mealy et al., in press), but there are no rigorous studies that systematically tested the benefit or sustainability of Scrambler versus a placebo treatment. The aim of the current study investigates use of Scrambler for treatment of central neuropathic pain in patients with NMOSD, given the substantial unmet need and lack of investigation into pharmacologic or non-pharmacologic intervention for pain management in this patient population.

Methods

We conducted a randomized single blind, sham-controlled trial in patients with NMOSD who have central neuropathic pain using Scrambler therapy. The central hypothesis that guided this study was that Scrambler therapy is an acceptable and feasible treatment that significantly reduces pain and improves co-occurring symptoms in patients with NMOSD.

Standard protocol approvals, registrations, and patient consents

We enrolled 22 patients with NMOSD (11 per arm) at the Johns Hopkins Neuromyelitis Optica Clinic. Participants with severe limitations to mobility or sight due to their disease were given the option to have study visits conducted in their homes. The protocol was approved through the Johns Hopkins Institutional Review Board (IRB00115699) and launched on March 2, 2018. Written informed consent was obtained from each participant prior to study enrollment.

The study was registered through ClinicalTrials.gov (NCT03452176). The Food and Drug Administration granted Scrambler therapy (FDA) 510(k) approval for acute, chronic and post-operative pain, "Scrambler ST 5 TENS Device," (K081255) in February 2009 (FDA, 2009).

Participants

Participants with self-reported neuropathic pain caused by NMOSD were recruited through the Johns Hopkins Neuromyelitis Optica Clinic. For participation eligibility, patients were aged 18 years or older with an NMOSD diagnosis based on the 2015 international consensus diagnostic criteria (Wingerchuk et al., 2015), regardless of anti-aquaporin 4 (AQP4) serostatus (Wingerchuk et al., 2007; Ruiz-Gaviria et al., 2015). For inclusion, neuropathic pain needed to be attributable to an inflammatory spinal cord lesion, indicated by MRI from a previous clinical myelitis event. Persistent pain needed to be rated at a level of 4 or higher on an 11-point numeric rating scale (NRS), with persistent pain defined by presence for >3 months. Patients needed to be stable in their disease, such that they had no spinal cord relapses within 6 months prior to enrollment. Patients were eligible to use any combination of standard of care medications for pain treatment, including anti-epileptic, antidepressant, opioid or non-steroidal anti-inflammatory medications, with no adjustments to the regimen within 30 days of enrollment. Patients with a known or suspected concomitant diagnosis of peripheral neuropathy were excluded. Patients with an ongoing concomitant central neurologic disorder were excluded, as were those who used an investigational agent for pain control within 30 days of enrollment, were pregnant or breastfeeding, were cognitively or mentally incompetent, or had implantable pain management or arrhythmia devices.

Randomization and Masking

Following consent and screening, participants were randomly assigned to receive Scrambler treatment versus sham at a 1:1 ratio for 10 consecutive weekdays. Recruitment was batched using a randomized block design stratifying across medication class (anti-epileptic, antidepressant, opioid or none) and pain level at screening (moderate 4-6, or severe 7-10) using blocks of four patients to promote similar distributions across groups in this small study. The rationale was to increase homogeneity between groups due to limited data that suggest response to Scrambler therapy may differ due to interference of medications used for pain (Moon et al., 2015). Randomization assignments were assigned by a third-party utilizing www.randomizer.org.

Scrambler therapy was administered via the GEOMC Pain Scrambler, model MC-5A. Electrodes were placed on participants receiving treatment within the dermatome above and below the level of injury, in a sufficiently sensitive area closest to the pain. For instance, if the patient had pain in the back from C3 to C8, a set of electrodes would be placed at C2 (above the pain) and T1 (below the pain.) Stimulation intensity was increased until a maximum tolerable threshold was reached without being painful, per the established protocol (Calmare Technologies Inc., 2008). If the patient felt a constant burn, sting or feeling of discomfort, electrodes were repositioned. The exact electrode positioning depended on the demarcation of the surface pain area, and analgesic response of the patient. Once the channel was regulated to the patient's maximum intensity, pain was assessed by asking the patient how s/he felt in the area of pain covered by the electrodes and adjusted for desired effect of reduced pain and/or analgesic response. Additional channel-pairs were similarly implemented as necessary based on size of pain area, up to 5 pairs in total. Electrodes remained in the established position and intensity for

35 minutes from the time of proper placement was instituted. As central pain is often more pervasive as compared with peripheral neuropathy, more than one area was often targeted.

For the sham group, small motors (<1 cm) which produce a vibratory sensation similar to a wearable activity tracker (i.e., FitBit) were connected to each electrode to simulate Scrambler stimulation but without electrical charge. Channel-pairs were similarly applied in a sufficiently sensitive dermatome closest to the pain, surrounding the level of spinal cord injury. The sham sensation was applied for 35 minutes.

For both groups, the Scrambler machine was kept behind a curtain to help preserve masking. The machine itself was turned on for all participants, though without emitting any stimulation in those receiving sham, so that the alert indicating termination of treatment would be heard by all participants regardless of treatment assignment. Because treatment effect has been shown to vary across technicians (Moon et al., 2015), one technician was trained in the proper delivery of Scrambler treatment and performed all interventions.

Study Objectives and Measures

Our primary objective was to determine if Scrambler therapy is an effective, acceptable, feasible and safe treatment of persistent central neuropathic pain. The primary outcome was effectiveness at the end of the 10-day treatment period. This was evaluated based on degree of improvement in pain, comparing the treatment group to sham. Prior to initiation of Scrambler therapy and at completion of treatment, patients were asked to rate their pain by the 11-point NRS score. Patients additionally reported NRS pain scores at 30- and 60- days following therapy completion to assess sustainability of treatment effect.

Feasibility of treatment was examined to determine whether the intervention was appropriate for this patient population, toward the effort of informing a larger, Phase III study. This was measured by assessing the following: 1) adherence to visit schedule and 2) response to the following question asked directly after completion of the 10-day treatment period: "Do you think you received treatment?" (Yes/No). Acceptability was measured by assessing response to the following question, also asked directly following the treatment course: "Would you want to continue treatment in clinic, if available?" (Yes/No).

Safety of the intervention was evaluated by comparing Adverse Events (AEs) and Serious Adverse Events (SAEs) in the treated versus sham groups. These were monitored and documented prior to initiation of each treatment daily, at termination of final treatment, and at 30- and 60-day follow-up.

Although not powered appropriately, an exploratory objective aimed to assess the relationship between improved pain and other co-occurring symptoms. Prior to initiation of Scrambler therapy, patients were asked to complete each of the following measurement tools to determine baseline pain severity and interference, anxiety, depression, and sleep disturbance, respectively: Brief Pain Inventory (BPI) (Cleeland, 2009), Neuro-QoL [Quality of Life in Neurological Disorders] Short Form v1.0 - Anxiety, Neuro-QoL Short Form v1.0 - Depression, and Neuro-QoL Short Form v1.0 - Sleep Disturbance (Cella et al., 2011). Measurement tools were accessed by participants via a secure online portal. Participants were provided with an alphanumeric code that enabled their responses to be linked to their demographic and clinical data in a confidential manner. Questionnaires were mailed to participants without internet access with a postage-paid envelope provided for return of questionnaires. Patients again completed all measurement tools at end of treatment, and at 30- and 60-days following end of treatment.

Statistical Analysis

Effectiveness was based on degree of improvement of pain and compared NRS pain scores in the treatment group and sham group using the Friedman One-Way Repeated Measure Analysis of Variance by Ranks test at baseline, following treatment, and at 30- and 60-day follow-up. Wilcoxon signed-rank testing was used to determine sustainability over time by comparing scores at baseline to those following treatment, at 30-day follow-up and at 60-day follow-up. A chi-squared analysis comparing the number of treated patients who thought they received treatment versus the number of sham patients who thought they received treatment was performed to determine if masking was effective.

The target sample size of 22 (11 per arm) was based on previous studies which suggest that the average pain value at baseline is at least 4 on the 0-10 NRS with a standard deviation of the original pain value expected to fall in the range of 1-1.5 in this patient population (Majithia et al., 2016; Park et al., 2017; Ricci et al., 2011; Pachman et al., 2015; Smith et al., 2010; Marineo et al., 2012). A conservative estimate of the standard deviation of the change across patients from Day 1 to Day 10 was approximately up to 2. With 11 patients in each arm and under these assumptions, we were able to detect a change of 2.5 points in the Scrambler group at 80% power, with a difference in proportions of 60% between the two groups.

As one measure of feasibility of treatment, adherence to visit schedule was ascertained. We report the number of patients in each group who were able to complete all treatments. Fisher's exact test was performed to assess if adherence is independent of group assignment. For each of the two survey questions used to assess feasibility and acceptability, as described above, a 95% confidence interval for the proportion of participants answering "Yes" was calculated.

Given the small number of patients in the study, exact binomial confidence intervals were calculated since normal distribution could not be assumed.

Descriptive statistics were used to report AEs and SAEs. Incidence and severity were compared between groups.

To explore the impact on co-occurring symptoms when intervening on pain, scores were tabulated for each of the following based on measurement tool data: anxiety, depression, sleep disturbance and pain interference. Friedman One-Way Repeated Measure Analysis of Variance by Ranks was tabulated for each symptom, comparing the change at baseline, following treatment, and at 30- and 60-day follow-up timepoints in each arm. A subanalysis was similarly conducted in those patients who "responded" to Scrambler treatment versus sham. Based on a cohort of adult patients with spinal cord injury who reported clinically meaningful change in pain over time (Hanley et al., 2006), "response" was defined as patients with a decrease in NRS pain scores of 1.80 points between baseline and end of treatment.

Demographic and clinical characteristics were compared between Scrambler and sham groups using Mann-Whitney *U* and Chi-squared testing, as appropriate.

Data Availability

Public Law 110-85 (also known as the FDA Amendments Act of 2007) mandates registration and results reporting of "applicable clinical trials" in ClinicalTrials.gov. We support efforts to promote data sharing toward the advancement of science and registered this clinical trial, providing trial design, eligibility criteria and outcomes measures.

Classification of Evidence

This study provides Class 1 evidence of Scrambler therapy use in patients diagnosed with NMOSD who have central neuropathic pain.

Results

Twenty-two patients (11 per arm) who were deemed eligible for participation in this clinical trial were enrolled, treated and received follow-up between March and December 2018 (Figure 1). Participants were treated with Scrambler therapy or sham. Most patients were female (91%) and African American (59%). All participants were seropositive for AQP4 IgG. The median baseline NRS pain level was 5 points for both the treatment and sham groups (mean=5.6). The median Expanded Disability Status Scale (EDSS) score was 6.0 and 4.5 for the treatment and sham groups, respectively. Patient characteristics were similar between groups (Table 1).

Effectiveness Outcomes

The effectiveness of Scrambler therapy was determined by the impact on pain over time in the treatment group compared to the sham group, as measured by the NRS pain score. NRS pain scores were recorded at baseline, immediately following treatment versus sham, and at 30- and 60-days following treatment versus sham. Following the 10-day protocol, Scrambler therapy resulted in a reduction in median NRS pain scores from 5.0 to 1.5 ($p<0.001$), whereas the sham condition resulted in a reduction in median NRS pain scores from 5.0 to 4.0 ($p=0.4239$) (Figure 2). In the Scrambler therapy arm, eight of 11 participants had a clinically meaningful improvement in pain, with four participants experiencing complete pain eradication immediately following the protocol, (Figure 3). NRS pain scores remained significantly decreased at 30 days in the Scrambler-treated group ($p=0.0195$). However, the effect was not sustained at 60 days

(p=0.0518). Because of this, a post hoc power calculation was conducted based on current study data to determine the sample size needed to detect a change in this secondary endpoint for use in a larger Phase III trial. It was determined that 29 patients per arm would be necessary, given a mean 60-day score of 4.07 in the Scrambler treated arm and 5.32 in the sham arm with a standard deviation of 1.89.

Feasibility/Acceptability Outcomes

There was no difference between groups in the number of participants who completed all treatments (p=0.22). All participants in the treatment arm completed all treatments, and two participants in the sham arm completed only 9 of 10 sessions: one patient experienced a family emergency and the other had a urinary tract infection that interfered with the trial. A chi-squared analysis revealed that masking of the intervention was adequate, as there was no difference found between those in the treated group who thought they received Scrambler therapy versus those in the sham group who thought they received therapy (p=0.20; 95% CI 0.91 to 5.04). Additionally, a chi-squared analysis also suggested that those who received the sham intervention were equally likely to want to continue treatments as those who received treatment (p=0.67; 95% CI 0.56 to 3.61).

Safety Outcome

All AEs were logged daily prior to and following each treatment, as well as at 30- and 60-day follow-up (Table 2). There were no SAEs reported during the 10-day treatment period among participants in either study arm. During follow-up, two SAEs were reported within the same patient: Patient 3 (sham arm) developed a port and bloodstream infection 30 days after completion of the 10-day sham course requiring hospitalization for IV antibiotic treatment.

Because the infection was unresolved, the patient was re-hospitalized 30 days later for IV antibiotics. Given the temporal profile and fact that the patient did not receive Scrambler treatment, these infections were not thought to be related to the study. Neither Scrambler therapy nor the sham condition resulted in increased pain severity in these trial participants.

Exploratory Outcome

The median depression T score in the treatment arm significantly decreased following treatment with Scrambler therapy (p=0.03). There were no significant decreases in anxiety (p=0.10), sleep disturbance (p=0.26) or pain interference (p=0.37) following Scrambler intervention (Figure 4). In the Scrambler therapy arm, eight participants had a clinically meaningful improvement in pain, based on a decrease in NRS pain score of 1.80 or greater. When considering only these patients, the change in median anxiety T scores becomes significant (p=0.02), while sleep disturbance and pain interference remain unchanged (p=0.64 & p=0.68, respectively). Among those in the sham arm, the median anxiety, depression and sleep disturbance T scores did not change over time (p=0.15, p=0.60, p=0.36, respectively). Four participants had a clinically meaningful improvement in pain in the sham arm. When considering only these patients, all symptoms remain unchanged over time.

Discussion

Results of this sham-controlled trial in patients with NMOSD demonstrate that Scrambler therapy is an effective and safe intervention for central neuropathic pain. Participants who received Scrambler therapy had a significant reduction in pain, as compared to those who received sham. This was sustained at 30 days following the treatment course. Notably, there was no difference in the number of patients who thought they were assigned to the treatment versus

sham groups, which suggests that any placebo effect was controlled for through the established sham intervention. To date, most research investigating the effect of Scrambler therapy on pain has involved open label trials for peripheral neuropathic pain management (Smith et al., 2017; Joo et al., 2017; Park et al., 2017; Kim et al., 2017; Sabato et al., 2005; Notaro et al., 2016). Four studies have utilized a random controlled design, including two unblinded prospective randomized trials that tested Scrambler therapy against an active comparator (Loprinzi et al., 2018; Marineo et al., 2012), and two that have applied a blinded, randomized, sham-controlled design. One involved patients with chemotherapy-induced peripheral neuropathy, which found no difference, when compared to Scrambler therapy placed on the back near the spine (n=14) (Campbell et al., 2013). In the second prospective, placebo-controlled trial, tested in patients diagnosed with low-back pain (n=30), the treatment group was found to have a significant reduction in pain compared to the control group (Starkweather et al., 2015). The sham group received Scrambler therapy, at what was thought to be subtherapeutic doses.

Results suggest the trial is feasible and acceptable. Adherence with the full program comprising 10 sequential weekday visits was similar in both groups, and there was no difference in the number of participants who completed the trial and follow up in both groups. Both groups also reported an interest in continuing treatments beyond the trial period indicating a strong desire for pain relief using non-medical therapies. Because many of our NMOSD participants were severely disabled and unable to commute to the clinic on a regular basis, we offered home treatment in both arms. This likely improved feasibility and protocol adherence and suggests that a study that enables home treatments would make NMOSD participant enrollment and retention easier for a larger study.

This is the first prospective, interventional trial of a therapy to treat pain in patients with NMOSD to be reported, as well as the first to investigate Scrambler therapy specifically for central neuropathic pain. The rationale for Scrambler use in patients with NMOSD involves the peripheral sensitization of non-myelinated ascending C fibers, the slightest stimulation of which are interpreted by the brain as persistent pain (Pellkofer et al., 2013). In addition to evidence that Scrambler therapy improves pain from peripheral neuropathy, investigation into Scrambler therapy in patients with central neuropathic pain syndromes has been limited to two case studies (hemorrhagic brainstem cavernoma and transverse myelitis) prior to our study, both of which reported improvement in pain (D'Amato et al., 2018; Mealy et al., in press).

Opioids are frequently employed for breakthrough therapy in patients with NMOSD given the severity and intensity of pain in this population. Doses and numbers of medications are often increased due to opioid tolerance, causing side effects, particularly at higher doses, which are independently associated with fatigue (Qian et al., 2012). With growing awareness of the dangers of polypharmacy, Scrambler therapy provides a non-pharmacologic option for central neuropathic pain treatment. Advancing alternative mechanisms for pain treatment including Scrambler therapy may allow for reduced medication dosing such that other symptoms with which the patient is already struggling are not exacerbated.

Recent research in chronic disease suggests that treating one symptom in isolation of other co-occurring symptoms does not impact QoL (Kim et al., 2013). However, small studies specific to patients with NMOSD indicate that treating pain may have the greatest impact on improving QoL (Mealy et al., 2016; Mealy et al., in press). While the current study did not measure QoL, the findings suggest that among those who responded to Scrambler therapy, intervening on pain decreases depression and anxiety, which may, in turn, impact QoL.

This study was limited by several factors. First, the design of this study was single-blinded due to the fact that the technician knew if treatment or sham was being delivered by necessity. To mitigate the bias this potentially introduced, measurement tools and survey data were collected by an unrelated study coordinator. Second, though patients were recruited using a randomized block design to mitigate risk of confounding effects from pain medication class based on previous data which reported that the type of medication may be predictive of response to Scrambler therapy (Moon et al., 2015), our study was not powered to sufficiently compare efficacy results across classes of pain medications since patients were often on multiple medications. Lastly, this study was not powered to effectively examine sustainability of treatment, which was not sustained through the 60-day follow-up period. However, the trend toward significance at 60 days (p=0.0518) suggests that a larger study that includes 29 patients per arm may uncover sustained effect. The effect that modifying pain through Scrambler therapy had on co-occurring symptoms was also limited by the sample size. The effectiveness, feasibility and safety profiles we report support the need for a larger Phase III study to further examine the effect of Scrambler on pain, co-occurring symptoms and quality of life in a larger NMOSD patient cohort.

Author contributions

MAM contributed to the conceptualization and design of the study, data collection and analysis, interpretation of data, and drafting/revising manuscript content. SLK contributed to the conceptualization and design of the study, data analysis, interpretation of data, and revising manuscript content. LJC contributed to data analysis, interpretation of data, and revising manuscript content. LT and RAS contributed to data collection and revising manuscript content.

JKA and MTN contributed to study design and revising manuscript content. TJS contributed to study design, data collection, interpretation of data, and revising manuscript content. ML contributed to the conceptualization and design of the study, data collection and analysis, interpretation of data, and drafting/revising manuscript content.

Acknowledgments

The authors would like to thank Giuseppe Marineo, PhD, and Stephen D'Amato, MD, as our expert Scrambler advisors throughout the study, DIS&L for supplying the GEOMC Pain Scrambler model MC-5A machine, Hugh M. Mealy for assembling and maintaining the sham device, and our patients for their contributions to this study.

References

Calmare Technologies, Inc. Calmare Model MC-5A Non-Invasive Pain Therapy Treatment User's Manual. 2008. Available from http://calmarett.com/media/pdf/User%20Manual_International%20Version_25Nov2008.pdf . Accessed September 6, 2016.

Campbell, T., Nimunkar, A.J., Eickhoff, J.C., Backonja, M., Cleary, J.F.… Yen TY. (2013). A randomized, double-blind study of "Scrambler" therapy versus sham for painful chemotherapy-induced peripheral neuropathy. *J Clin Oncol. 31*:suppl; abstr 9635.

Cella, D., Nowinski, C., Peterman, A., Victorson, D., Miller, D., Lai, J. S., & Moy, C. (2011). The neurology quality-of-life measurement initiative. Archives of Physical Medicine and Rehabilitation, 92(10 Suppl), S28-36. doi:10.1016/j.apmr.2011.01.025 [doi]

Cleeland, C. S., Gonin, R., Hatfield, A. K., Edmonson, J. H., Blum, R. H., Stewart, J. A., & Pandya, K. J. (1994). Pain and its treatment in outpatients with metastatic cancer. *The New England Journal of Medicine, 330*(9), 592-596. doi:10.1056/NEJM199403033300902 [doi]

D'Amato, S. J., Mealy, M. A., Erdek, M. A., Kozachik, S., & Smith, T. J. (2018). Scrambler therapy for the treatment of chronic central pain: A case report. *A&A Practice, 10*(12), 313-315. doi:10.1213/XAA.0000000000000695 [doi]

Definition of classes of evidence (CoE) and overall strength of evidence (SoE). (2014). *Evidence-Based Spine-Care Journal, 5*(1), 71-0034-1373841. doi:10.1055/s-0034-1373841 [doi]

Eaneff, S., Wang, V., Hanger, M., Levy, M., Mealy, M. A., Brandt, A. U., . . . Wicks, P. (2017). Patient perspectives on neuromyelitis optica spectrum disorders: Data from the PatientsLikeMe online community. *Multiple Sclerosis and Related Disorders, 17*, 116-122. doi:S2211-0348(17)30164-5 [pii]

Food and Drug Administration. 501(k) Summary for the Competative Technologies, Inc. Scrambler Therapy MC-5A TENS Device. (2009). https://www.accessdata.fda.gov/cdrh_docs/pdf8/K081255.pdf. Accessed 10/14/2016.

Hanley MA, Jensen MP, Ehde DM, Robinson LR, Cardenas DD, Turner JA, Smith DG. (2006). Clinically significant change in pain intensity ratings in persons with spinal cord injury or amputation. *Clin J Pain, 22*(1):25-31.

Hollinger, K. R., Franke, C., Arenivas, A., Woods, S. R., Mealy, M. A., Levy, M., & Kaplin, A. I. (2016). Cognition, mood, and purpose in life in neuromyelitis optica spectrum disorder. *Journal of the Neurological Sciences, 362*, 85-90. doi:10.1016/j.jns.2016.01.010 [doi]

Joo, S. Y., Cho, Y. S., Cho, S. R., Kym, D., & Seo, C. H. (2017). Effects of pain scrambler therapy for management of burn scar pruritus: A pilot study. *Burns: Journal of the International Society for Burn Injuries, 43*(3), 514-519. doi:S0305-4179(16)30409-0 [pii]

Kanamori, Y., Nakashima, I., Takai, Y., Nishiyama, S., Kuroda, H., Takahashi, T., . . . Itoyama, Y. (2011). Pain in neuromyelitis optica and its effect on quality of life: A cross-sectional study. *Neurology, 77*(7), 652-658. doi:10.1212/WNL.0b013e318229e694 [doi]

Kashyap, K., Joshi, S., Vig, S., Singh, V., & Bhatnagar, S. (2017). Impact of scrambler therapy on pain management and quality of life in cancer patients: A study of twenty cases. *Indian Journal of Palliative Care, 23*(1), 18-23. doi:10.4103/0973-1075.197948 [doi]

Kim, H. J., Abraham, I., & Malone, P. S. (2013). Analytical methods and issues for symptom cluster research in oncology. *Current Opinion in Supportive and Palliative Care, 7*(1), 45-53. doi:10.1097/SPC.0b013e32835bf28b [doi]

Kim, Y. N., Lee, D. K., & Lee, H. J. (2017). Effect of pain scrambler therapy on antineuralgic pain and quality of life after shingles. *Journal of Physical Therapy Science, 29*(6), 1113-1115. doi:10.1589/jpts.29.1113 [doi]

Kong, Y., Okoruwa, H., Revis, J., Tackley, G., Leite, M. I., Lee, M., . . . Palace, J. (2016). Pain in patients with transverse myelitis and its relationship to aquaporin 4 antibody status. *Journal of the Neurological Sciences, 368*, 84-88. doi:10.1016/j.jns.2016.06.041 [doi]

Loprinzi, C. L., Le-Rademacher, J., Majithia, N., McMurray, R., Bendel, M.… Smith, T. J. (2018). Scrambler therapy for established chemotherapy-induced neuropathy: A randomized phase II trial. *J Clin Oncol. 36*(15): 10016-10016.

Majithia, N., Smith, T. J., Coyne, P. J., Abdi, S., Pachman, D. R., Lachance, D., . . . Loprinzi, C. L. (2016). Scrambler therapy for the management of chronic pain. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer, 24*(6), 2807-2814. doi:10.1007/s00520-016-3177-3 [doi]

Marineo, G., Iorno, V., Gandini, C., Moschini, V., & Smith, T. J. (2012). Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: Results of a pilot, randomized, controlled trial. *Journal of Pain and Symptom Management, 43*(1), 87-95. doi:10.1016/j.jpainsymman.2011.03.015 [doi]

Mealy, M. A., Newsome, S. D., Kozachik, S. L., Levy, M., Smith, T. J. (2018). Scrambler Therapy for Treatment-Resistant Central Neuropathic Pain in a Patient with Transverse Myelitis: A Case Report. *Int J MS Care.* In-Press. Online ahead of print: https://doi.org/10.7224/1537-2073.2017-083.

Mealy, M. A., Simpson, A., Levy, M. (2016). Comparing the Burden of Symptom Severity among Autoimmune Diseases affecting the Spinal Cord. In 32nd European Committee for Treatment and Research in Multiple Sclerosis Annual Congress; September 14-17; London, UK. Abstract A-777-0039-02305.

Mealy, M. A., Boscoe, A., Caro, J., Levy, M. (2018). Assessment of Patients with Neuromyelitis Optica Spectrum Disorder Using EQ-5D. *Int J MS Care.* Online ahead of print: doi.org/10.7224/1537-2073.2017-076.

Moon, J. Y., Kurihara, C., Beckles, J. P., Williams, K. E., Jamison, D. E., & Cohen, S. P. (2015). Predictive factors associated with success and failure for calmare (scrambler) therapy: A multicenter analysis. *The Clinical Journal of Pain, 31*(8), 750-756. doi:10.1097/AJP.0000000000000155 [doi]

Moore, P., Methley, A., Pollard, C., Mutch, K., Hamid, S., Elsone, L., & Jacob, A. (2016). Cognitive and psychiatric comorbidities in neuromyelitis optica. *Journal of the Neurological Sciences, 360*, 4-9. doi:10.1016/j.jns.2015.11.031 [doi]

Notaro, P., Dell'Agnola, C. A., Dell'Agnola, A. J., Amatu, A., Bencardino, K. B., & Siena, S. (2016). Pilot evaluation of scrambler therapy for pain induced by bone and visceral metastases and refractory to standard therapies. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer, 24*(4), 1649-1654. doi:10.1007/s00520-015-2952-x [doi]

Oh, J., & Levy, M. (2012). Neuromyelitis optica: An antibody-mediated disorder of the central nervous system. *Neurology Research International, 2012*, 460825. doi:10.1155/2012/460825 [doi]

Pachman, D. R., Weisbrod, B. L., Seisler, D. K., Barton, D. L., Fee-Schroeder, K. C., Smith, T. J., . . . Loprinzi, C. L. (2015). Pilot evaluation of scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer, 23*(4), 943-951. doi:10.1007/s00520-014-2424-8 [doi]

Park, H. S., Sin, W. K., Kim, H. Y., Moon, J. Y., Park, S. Y., Kim, Y. C., & Lee, S. C. (2013). Scrambler therapy for patients with cancer pain - case series -. *The Korean Journal of Pain, 26*(1), 65-71. doi:10.3344/kjp.2013.26.1.65 [doi]

Pellkofer, H. L., Havla, J., Hauer, D., Schelling, G., Azad, S. C., Kuempfel, T., . . . Huge, V. (2013). The major brain endocannabinoid 2-AG controls neuropathic pain and mechanical

hyperalgesia in patients with neuromyelitis optica. *PloS One, 8*(8), e71500. doi:10.1371/journal.pone.0071500 [doi]

Qian, P., Lancia, S., Alvarez, E., Klawiter, E. C., Cross, A. H., & Naismith, R. T. (2012). Association of neuromyelitis optica with severe and intractable pain. *Archives of Neurology, 69*(11), 1482-1487. doi:1355367 [pii]

Ricci, M., Pirotti, S., Scarpi, E., Burgio, M., Maltoni, M., Sansoni, E., & Amadori, D. (2012). Managing chronic pain: Results from an open-label study using MC5-A calmare(R) device. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer, 20*(2), 405-412. doi:10.1007/s00520-011-1128-6 [doi]

Ruiz-Gaviria, R., Baracaldo, I., Castaneda, C., Ruiz-Patino, A., Acosta-Hernandez, A., & Rosselli, D. (2015). Specificity and sensitivity of aquaporin 4 antibody detection tests in patients with neuromyelitis optica: A meta-analysis. *Multiple Sclerosis and Related Disorders, 4*(4), 345-349. doi:10.1016/j.msard.2015.06.003 [doi]

Sabato, A. F., Marineo, G., & Gatti, A. (2005). Scrambler therapy. *Minerva Anestesiologica, 71*(7-8), 479-482.

Shi, Z., Chen, H., Lian, Z., Liu, J., Feng, H., & Zhou, H. (2016). Factors that impact health-related quality of life in neuromyelitis optica spectrum disorder: Anxiety, disability, fatigue and depression. *Journal of Neuroimmunology, 293*, 54-58. doi:10.1016/j.jneuroim.2016.02.011 [doi]

Smith, T., Cheville, A. L., Loprinzi, C. L., & Longo-Schoberlein, D. (2017). Scrambler therapy for the treatment of chronic post-mastectomy pain (cPMP). *Cureus, 9*(6), e1378. doi:10.7759/cureus.1378 [doi]

Smith, T. J., Auwaerter, P., Knowlton, A., Saylor, D., & McArthur, J. (2017). Treatment of human immunodeficiency virus-related peripheral neuropathy with scrambler therapy: A case report. *International Journal of STD & AIDS, 28*(2), 202-204. doi:10.1177/0956462416656688 [doi]

Smith, T. J., Coyne, P. J., Parker, G. L., Dodson, P., & Ramakrishnan, V. (2010). Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A calmare(R)) for chemotherapy-induced peripheral neuropathy. *Journal of Pain and Symptom Management, 40*(6), 883-891. doi:10.1016/j.jpainsymman.2010.03.022 [doi]

Starkweather, A. R., Coyne, P., Lyon, D. E., Elswick, R. K.,Jr, An, K., & Sturgill, J. (2015). Decreased low back pain intensity and differential gene expression following calmare(R): Results from a double-blinded randomized sham-controlled study. *Research in Nursing & Health, 38*(1), 29-38. doi:10.1002/nur.21632 [doi]

Wingerchuk, D. M., Banwell, B., Bennett, J. L., Cabre, P., Carroll, W., Chitnis, T., . . . International Panel for NMO Diagnosis. (2015). International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology, 85*(2), 177-189. doi:10.1212/WNL.0000000000001729 [doi]

Wingerchuk, D. M., Lennon, V. A., Lucchinetti, C. F., Pittock, S. J., & Weinshenker, B. G. (2007). The spectrum of neuromyelitis optica. *The Lancet.Neurology, 6*(9), 805-815. doi:S1474-4422(07)70216-8 [pii]

Zhao, S., Mutch, K., Elsone, L., Nurmikko, T., & Jacob, A. (2014). Neuropathic pain in neuromyelitis optica affects activities of daily living and quality of life. *Multiple Sclerosis (Houndmills, Basingstoke, England), 20*(12), 1658-1661. doi:10.1177/1352458514522103 [doi]

Figure 1: CONSORT flow diagram

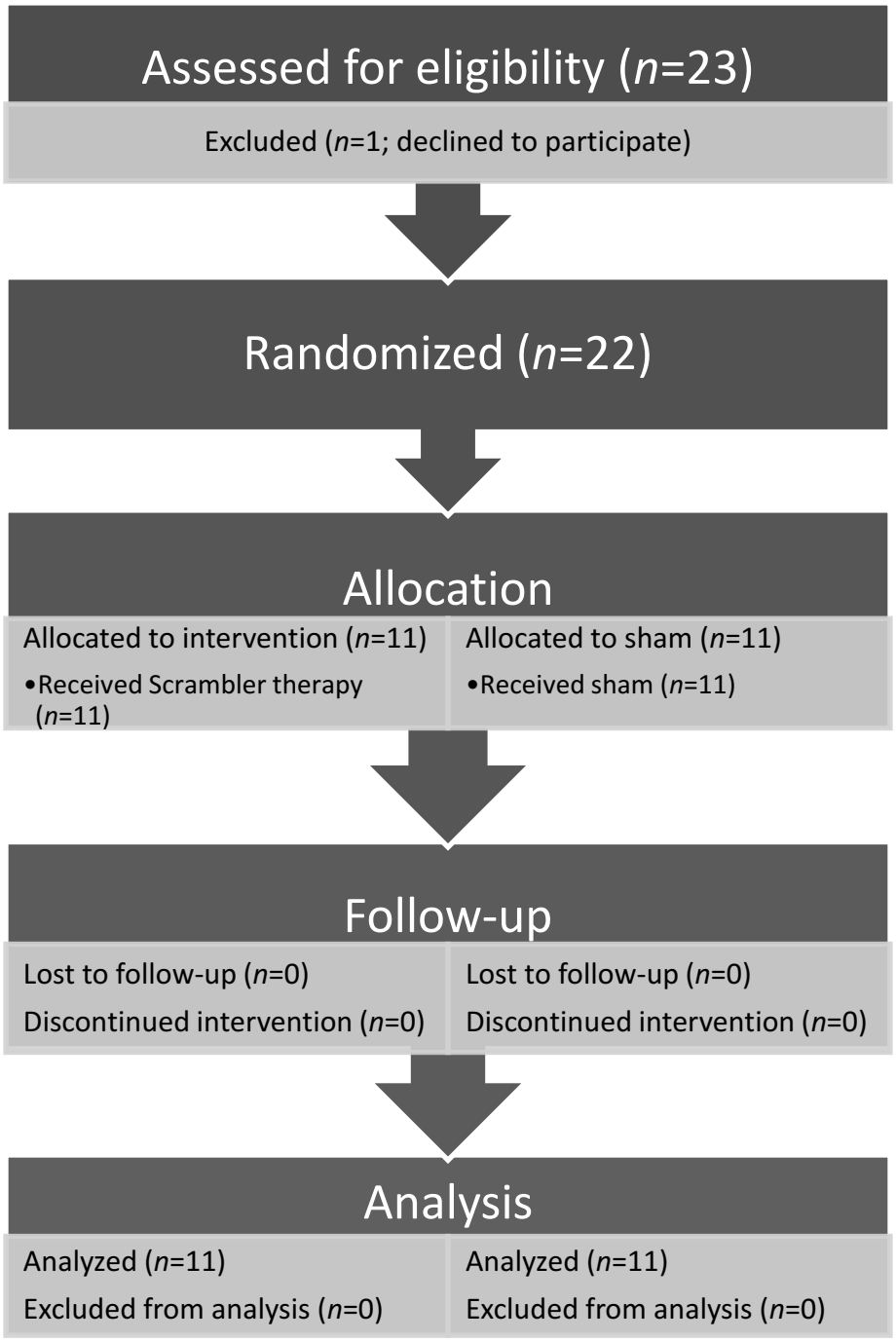


Figure 2: Box and whisker plots depicting median change in NRS pain scores across time points in A) Scrambler treated and B) sham arms.

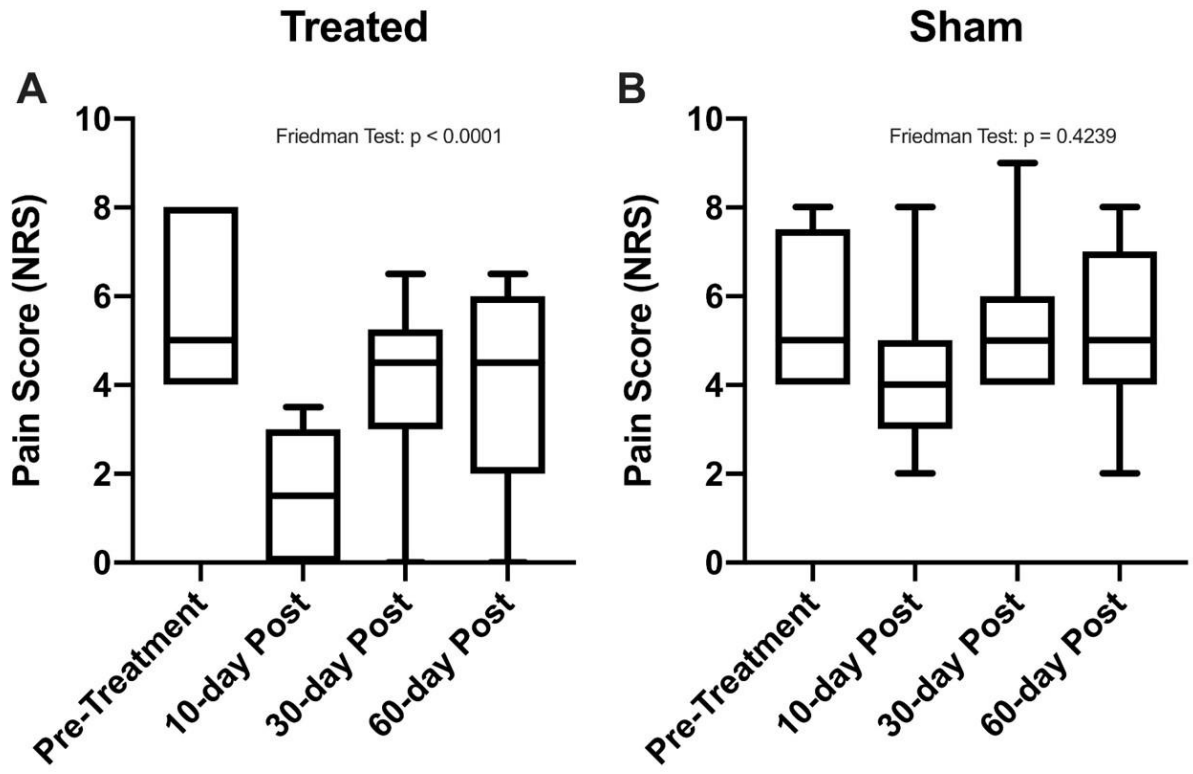
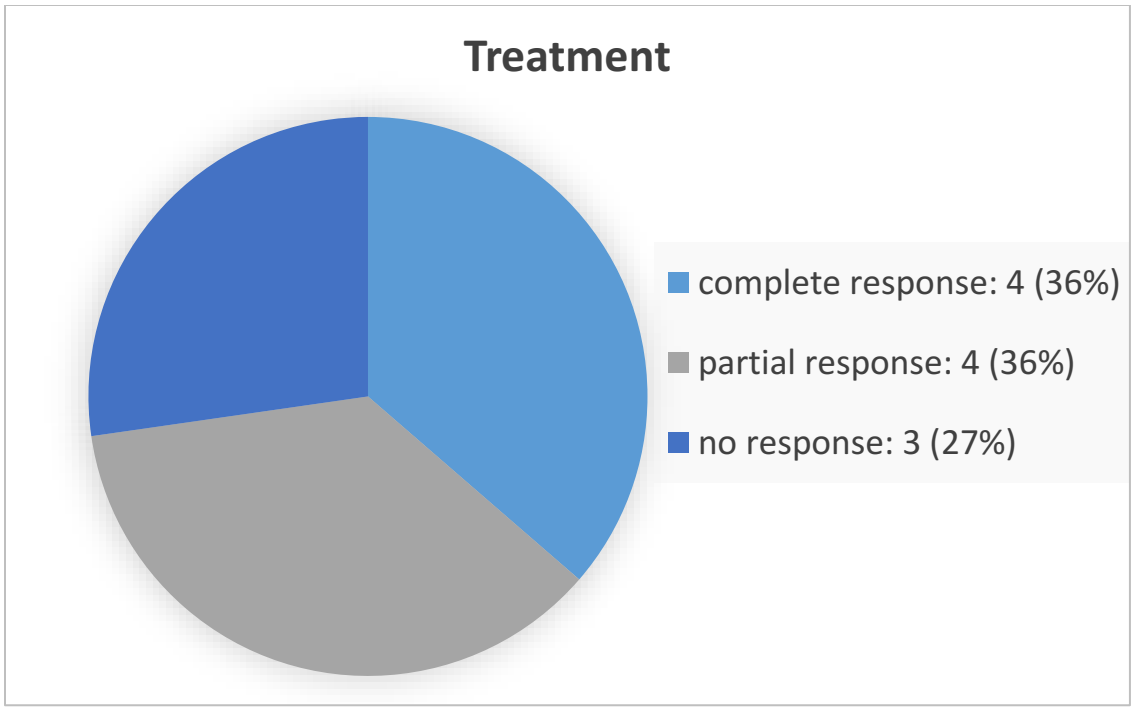


Figure 3: Patient response by arm at end of 10-day treatment. Complete response (NRS=0), partial response (decrease in NRS >1.8 but not rated at 0), no response (decrease in NRS $\leq$1.8):

A) Scrambler therapy intervention. Median decrease in NRS was 4 points in "partial responders" and 1.5 points in "non-responders".

B) Sham intervention. Median decrease in NRS was 3.5 points in "partial responders" and -0.5 point in "non-responders".


Treatment
complete response: 4 (36%)
partial response: 4 (36%)
no response: 3 (27%)

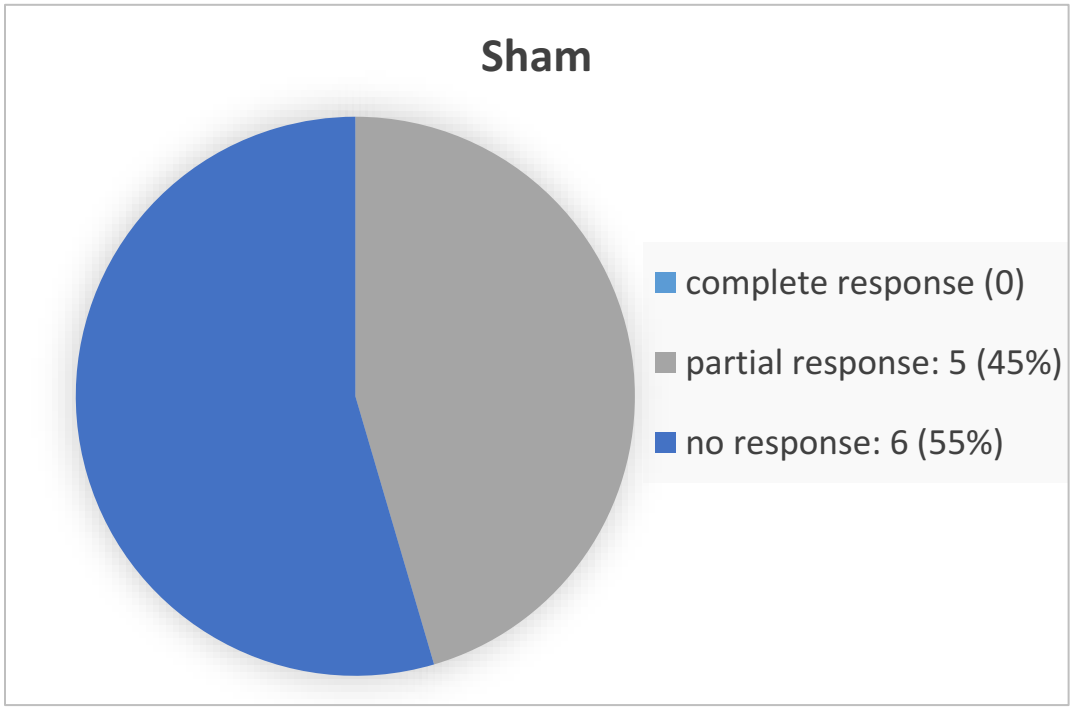

Sham
complete response (0)
partial response: 5 (45%)
no response: 6 (55%)

Figure 4: Box and whisker plots depicting median change in A) depression, B) anxiety, C) sleep disturbance and D) pain interference scores for Scrambler treated and sham arms.

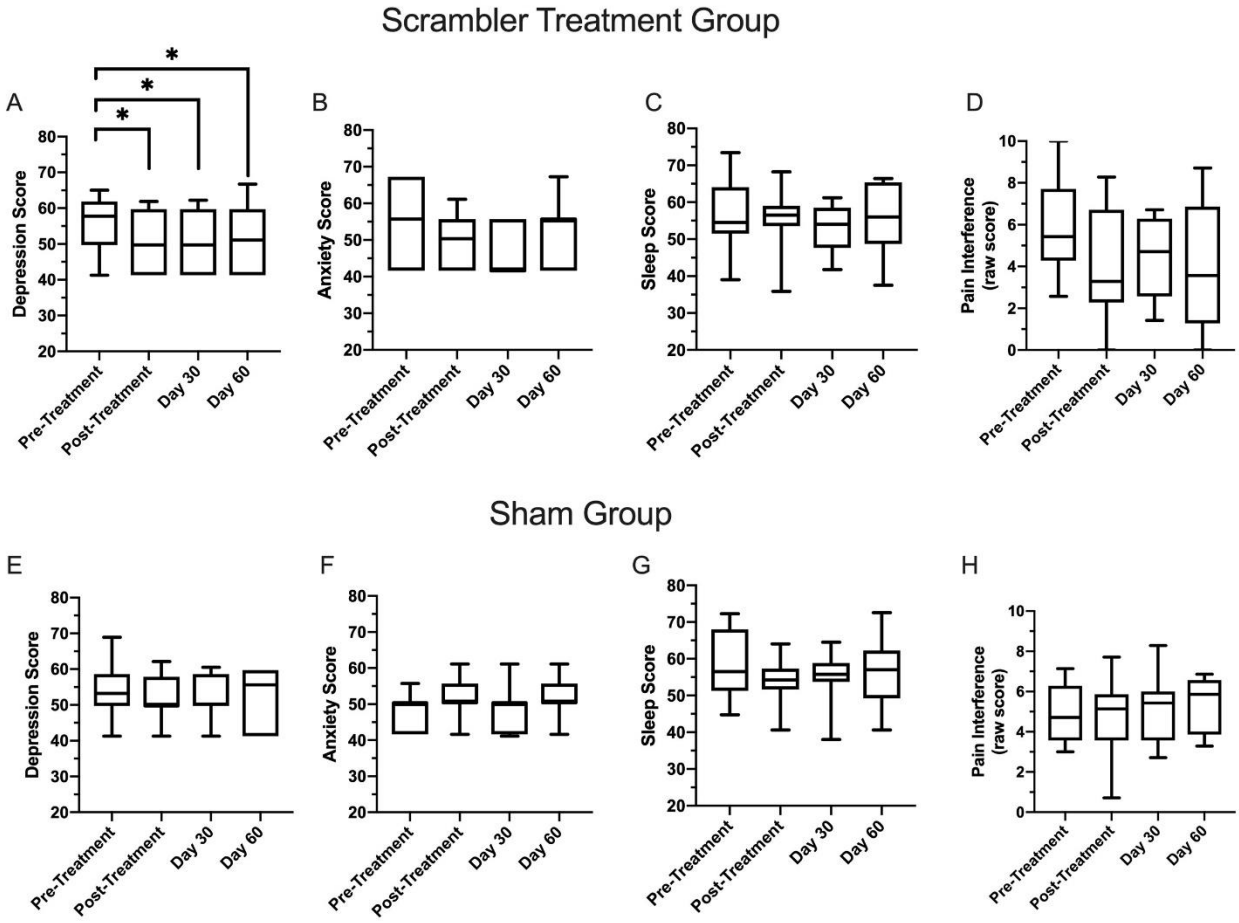


Table 1. Demographic and clinical characteristics of participants

	Treatment	**Sham**	***p*-value**
Participants	11	11	1.0
Female sex	10 (91%)	10 (91%)	1.0
Race			
African American	6 (55%)	7 (64%)	0.89
Caucasian American	3 (27%)	4 (36%)	
Other	2 (18%)	0 (0%)	
Age			
Median (IQR)	56.2 (7.2)	57.5 (13.8)	0.94
Mean (SD)	55.2 (9.6)	52.8 (14.9)	
Disease duration			
Median (IQR)	11.0 (12.8)	6.0 (7.6)	0.34
Mean (SD)	11.7 (8.8)	7.6 (5.6)	
Delay in diagnosis			
Median (IQR)	0.5 (8.8)	0.3 (1.0)	0.29
Mean (SD)	4.3 (5.3)	1.0 (1.5)	
AQP4* serostatus			
Positive	11 (100%)	11 (100%)	1.0
EDSS* Score			
Median (IQR)	6.0 (3.0)	4.5 (3.0)	0.63
Mean (SD)	5.1 (2.3)	4.7 (2.0)	
Baseline NRS* pain rating			
Median (IQR)	5.0 (2.8)	5.0 (3.2)	0.76
Mean (SD)	5.6 (1.7)	5.6 (1.8)	
Pain medication regimen			
Treated	7 (64%)	8 (73%)	0.65
AEDs*	6	8	
Anti-depressants	5	3	
Opioids	3	3	
Untreated	4 (36%)	3 (27%)	

*AQP4=aquaporin 4; EDSS=Expanded Disability Status Scale; NRS=numeric rating scale; AEDs=antiepileptic drugs

Table 2. Adverse events

	Pt #	Start of Treatment versus Sham	End of Treatment versus Sham	30-day Follow-up	60-day Follow-up	Event	AE Start Date	AE End Date	Severity	Action Taken	Related/ Not related to treatment
Treatment	**01**	3/12/2018	3/26/2018	4/25/18	5/31/18	Charles Bonnet Syndrome	3/21/18 (during treatment phase)	ongoing	Moderate	None	Not related
	02	4/2/2018	4/13/2018	5/14/18	6/10/18	None	N/A	N/A	N/A	N/A	N/A
	05	6/4/2018	6/15/2018	7/14/18	8/11/18	None	N/A	N/A	N/A	N/A	N/A
	06	6/11/2018	6/22/2018	7/23/18	8/17/18	None	N/A	N/A	N/A	N/A	N/A
	07	7/9/2018	7/20/2018	8/24/18	9/20/18	Insomnia	7/10/18 (during treatment phase)	7/11/18	Mild	None	Not related
	09	7/16/2018	7/27/2018	8/27/18	10/10/18	Sensitivity to electrode adhesive	7/16/18 (during treatment phase)	7/27/18	Moderate	None	Related
	10	7/23/2018	8/3/2018	8/30/18	9/28/18	None	N/A	N/A	N/A	N/A	N/A
	11	8/6/2018	8/17/2018	9/27/18	10/15/18	None	N/A	N/A	N/A	N/A	N/A
	17	9/10/2018	9/21/2018	10/23/18	12/1/18	None	N/A	N/A	N/A	N/A	N/A

	19	9/24/2018	10/5/2018	11/10/18	12/4/18	None	N/A	N/A	N/A	N/A	N/A
	22	10/8/2018	10/19/2018	11/28/18	12/20/18	None	N/A	N/A	N/A	N/A	N/A
Sham	**3**	4/30/2018	5/11/2018	6/21/18	7/19/18	Bloodstream/ port infection	6/10/18 (during follow-up)	6/17/18	Severe	Admission for IV ABX	Not related
						Bloodstream infection	7/8/18 (during follow-up)	7/18/18	Severe	Admission for IV ABX	Not related
	4	5/7/2018	5/18/2018	6/18/18	7/13/18	None	N/A	N/A	N/A	N/A	N/A
	8	7/9/2018	7/20/2018	8/23/18	9/19/18	None	N/A	N/A	N/A	N/A	N/A
	12	7/23/2018	8/3/2018	9/10/18	10/16/18	None	N/A	N/A	N/A	N/A	N/A
	13	8/6/2018	8/17/2018	9/16/18	10/15/18	UTI	9/27/18 (during follow-up)	10/1/18	Moderate	Oral ABX	Not related
	14	8/20/2018	8/31/2018	10/15/18	11/7/18	None	N/A	N/A	N/A	N/A	N/A
	15	8/20/2018	8/31/2018	10/3/18	11/8/18	None	N/A	N/A	N/A	N/A	N/A
	16	9/3/2018	9/19/2018	10/18/18	11/19/18	None	N/A	N/A	N/A	N/A	N/A
	18	9/10/2018	9/21/2018	11/6/18	11/29/18	UTI	9/12/18 (during treatment phase)	9/14/18	Moderate	Oral ABX	Not related
	20	9/24/2018	10/5/2018	11/8/18	12/3/18	None	N/A	N/A	N/A	N/A	N/A
	21	9/24/2018	10/5/2018	11/15/18	12/5/18	None	N/A	N/A	N/A	N/A	N/A

*AE=adverse events; ABX=antibiotics; UTI=urinary tract infection

Chapter 4: Pain severity associates with poor quality of life in patients with neuromyelitis optica spectrum disorder (Manuscript 3)

Maureen A. Mealy, RN, PhD

Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Lauren Totonis

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Lawrence J. Cook, PhD

University of Utah, Department of Pediatrics, Salt Lake City, UT, USA

Ruth Andrea Salazar

Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA

Thomas J. Smith, MD

Johns Hopkins University School of Medicine, Department of Oncology, Baltimore, MD, USA

Jerilyn K. Allen, PhD, RN

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Marie T. Nolan, PhD, RN

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Sharon L. Kozachik, PhD, RN

Johns Hopkins University School of Nursing, Baltimore, MD, USA

Michael Levy, MD, PhD

Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA

Massachusetts General Hospital and Harvard Medical School, Department of Neurology, Boston, MA, USA

Abstract

Pain is a highly prevalent and severely disabling component of neuromyelitis optica spectrum disorder (NMOSD) that affects quality of life. The aim of this study was to determine the impact of pain on other co-occurring symptoms in persons with NMOSD. This cross-sectional analysis investigates the impact of pain on other symptoms that occur in patients with NMOSD, including anxiety, depression and sleep disturbance, as well as QoL. Seventy-two participants who were obtained through convenience sampling completed each of the following surveys to determine pain, health-related QoL, anxiety, depression and sleep disturbance, respectively: Brief Pain Inventory (BPI), Short Form-36 Health Inventory (SF-36), Neuro-QoL [Quality of Life in Neurological Disorders] Short Form v1.0 – Anxiety, Neuro-QoL Short Form v1.0 – Depression, and Neuro-QoL Short Form v1.0 - Sleep Disturbance. Pain was shown to correlate with physical components of QoL, fatigue, anxiety and sleep disturbance. However, degree of anxiety and sleep disturbance were similar in this patient cohort when compared to normative data. These data add to the body of evidence that pain may be the primary contributor of components that lead to poor QoL in patients with NMOSD.

Pain severity associates with poor quality of life in patients with neuromyelitis optica spectrum disorder

Neuromyelitis optica spectrum disorder (NMOSD) is a recurrent autoimmune disease that primarily targets the optic nerves and spinal cord, leading to blindness and immobility. Neuropathic pain due to inflammatory damage of the spinal cord is a highly prevalent and disabling component of the disease, with 83-91% of patients reporting its presence in descriptive studies (Kanamori et al., 2011; Qian et al., 2012; Pellkofer et al., 2013). Half of patients with NMOSD characterize their pain as severe and two thirds report being in constant pain (Zhao et al., 2014; Pellkofer et al., 2013). Research on the impact of persistent pain on quality of life (QoL) in NMOSD has found that pain is associated with depression, reduced enjoyment of life, and increased difficulty with ambulation (Mutch et al., 2014; Pellkofer et al., 2013; Zhao et al., 2014). Pain, mood, and mobility are the best predictors of poor QoL, and pain may be the strongest independent predictor (Kong et al., 2016; Mealy et al., 2018). In fact, pain predicts poor QoL better than disability, despite the profound impact NMOSD is known to have on neurologic function (Kong et al., 2016).

Treating multiple interrelated symptoms is more likely to improve QoL in chronic diseases (Kim et al., 2013). However, researchers are just beginning to understand the complexity of such relationships among symptoms and their effect on QoL in NMOSD. Preliminary evidence prompted the need to fully explore the interrelatedness of these frequently-occurring symptoms in NMOSD, and their effect on QoL. Because of its pervasiveness, investigating the impact of pain on these co-occurring symptoms, including anxiety, depression and sleep disturbance, as well as QoL, may offer health care providers a deeper understanding of how to approach comprehensive symptom management in this population.

Methods

This is a cross-sectional descriptive analysis of symptoms data collected from patients diagnosed with NMOSD. Participants were recruited through the Johns Hopkins NMO Clinic and through a social media support group for patients with NMOSD. All patients aged 18 years and older who fulfilled the 2015 International Panel for NMO Diagnosis (IPND) criteria were eligible for participation (Wingerchuk et al., 2015), regardless of pain status. The study was broadly presented to potential participants as an investigation into symptoms experienced by patients with NMOSD, so as to not deter data capture from patients who are pain-free. Following written informed consent, health records were obtained for review and data acquisition. A neurologist (ML) confirmed the diagnosis in those patients recruited through the social media site who were not evaluated in person at Johns Hopkins. Demographic and clinical data were extracted from all patient records. Participants were asked to access a secure online portal to complete a series of surveys and were provided with an alphanumeric code that enabled the study team to link participants' data in a confidential manner. For this cross-sectional assessment, participants completed each of the following surveys to determine pain, health-related QoL, anxiety, depression and sleep disturbance, respectively: Brief Pain Inventory (BPI; Cleeland, 2009), Short Form-36 Health Inventory (SF-36; Ware, Snow, & Kosinski, 1994), Neuro-QoL [Quality of Life in Neurological Disorders] Short Form v1.0 – Anxiety, Neuro-QoL Short Form v1.0 – Depression, and Neuro-QoL Short Form v1.0 - Sleep Disturbance (Cella et al., 2011). The study was approved by Johns Hopkins Institutional Review Board (IRB00065696).

Measurement Tools

BPI was an initiative of the National Cancer Institute and the World Health Organization in response to the need for better capture of the severity and impact of cancer pain and as a way to quantify improvement in pain after changes to analgesic therapy were made (Cleeland, 2009). It has been validated in dozens of persistent pain conditions and is among the most widely used tools in NMOSD research to date (Zhao et al., 2014; Kanamori et al., 2011). Separate scores for pain severity, based on a patient-reported 11-point numeric rating scale (NRS), and pain interference can be tabulated. Pain interference measures the patient-reported consequences of pain on relevant aspects of one's life, including the extent to which pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep (Cleeland, 2009). Both the pain severity and interference scales are scored from 0 to 10, where 0 indicates no pain/pain interference, and these dimensions grow increasingly worse as they approach ten.

The Medical Outcomes Study Short Form-36 Health Inventory (SF-36) is a patient-reported survey of overall patient health-related quality of life for which normative data are available (McHorney, Ware, Lu, & Sherbourne, 1994). It has been widely used for QoL assessment in chronic conditions, including in NMOSD research (Qian et al., 2012; Zhao et al., 2013; Pellkofer et al., 2014; Kanamori et al., 2011). Scores for eight sub-scales can be tabulated, and include physical components (physical function, physical role limitations, pain), mental components (emotional role limitations, emotional wellbeing, social function), and general components (energy/fatigue, general health) (Ware, 1994). Unlike with other measures, higher scores represent better functioning.

Neuro-QoL was established by the National Institutes of Health and is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults

and children living with neurological conditions (Cella et al., 2011). For data analysis, raw scores are rescaled into T-score distributions in order to standardize scores with a mean of 50 and a standard deviation of 10 for data analysis. A higher T-score represents more of the concept being measured, i.e., worse anxiety, depression, sleep disturbance. Normative data for anxiety and depression were derived based on the general U.S. population, and sleep disturbance was derived based on clinical populations (Ware, 1994).

Statistical Analysis

For this analysis, patients were binned into three categories based on their BPI pain severity score, mild (0-2), moderate (3-6) and severe (7-10). Non-parametric descriptive statistics were utilized to report demographic and clinical characteristics of the cohort. Each of the eight sub-scales of the SF-36 and all measures of co-occurring symptoms, as described above, were converted into a quantifiable score (Ware, 1994; Cleeland et al., 2009; NINDS User Manual Neuro-QoL, 2015). Patients were compared across the pain severity categories (mild, moderate and severe) for impact on QoL functionality and degree of anxiety, depression, sleep disturbance and pain interference using Kruskal-Wallis One-Way Analysis of Variance. Mean scores for the Neuro-QoL measurements of anxiety, depression and sleep disturbance in this cohort of patients with NMOSD were additionally compared with established normative data from general or clinical populations using two-sample *t*-tests. A global SF-36 score averaged the eight sub-scales and was used for a post hoc analysis to compare functioning across pain severity categories. Once a difference between two or more pain severity categories was established via Kruskal-Wallis testing, a Dunn's multiple comparisons test uncovered where these differences existed.

Results

Seventy-two patients met study criteria and provided complete data sets. Ten additional patients were screened but were ineligible for participation due to failure to meet the 2015 IPND criteria. As expected, most participants were female (90.3%). Median age at the time of data capture was 56.1 years. Ninety percent of this cohort was seropositive for the highly specific aquaporin 4 (AQP4) antibody associated with NMOSD. Disease duration was a median 6.0 years and delay in diagnosis was a median 6 months. Eighty-nine percent of patients reported some degree of pain, with 22 (31%) participants binned into the category containing patients with no to low pain, 23 (32%) participants in the moderate pain severity category and 27 (37%) participants in the high pain severity category. The degree of pain was independent of a history of myelitis, duration of disease, AQP4 serostatus and delay in diagnosis. Demographic and clinical profiles were similar across categories (Table 1).

Among the SF-36 sub-scales, those in the higher pain severity category were more likely to endorse lower functioning for all three physical components: physical mobility (p=0.01), physical role limitations (p=0.008), and, as expected, pain (p=0.0005) (Table 2). The effect of pain severity on SF-36 sub-scales that measure general components of functionality were split, such that those with higher pain severity endorsed low functioning due to energy/fatigue (p=0.008), but this was not the case for general health (p=0.058). Although the mental components of the SF-36 subscales did not significantly vary across different pain severity categories, there was a trend towards worsening emotional role limitations, wellbeing and social function with increasing pain severity. Given that there was a difference in functioning across pain severity categories, a post hoc analysis was conducted using a global SF-36 score. A significant difference in functioning was found between 2 or more pain severity categories (p=0.00143). Specifically, the difference was observed between low and moderate pain severity

categories (p=0.048) as well as low and high (p=0.0006), but not between moderate and high pain categories (p=0.413).

Patients in the moderate and high pain severity categories also reported more anxiety (p=0.05) and sleep disturbance (p=0.001) on the Neuro-QoL assessment, and pain interference increased with pain severity as well (p<0.0001). Depression was similar across pain severity categories (p=0.115) (Table 3). While pain severity worsens the physical impact, patients with NMOSD do not have higher rates of depression, anxiety or sleep disturbance compared with available normative data (Ware et al., 1994) (Table 4).

Discussion

Our study, in a cohort of patients with a median duration of disease of 6 years, is among the largest descriptive studies to assess the relationship of pain with co-occurring symptoms and components of quality of life in NMOSD. Results indicate that pain is present in the vast majority of patients with NMOSD, 89%, which concurs with previous investigations (Qian et al., 2012; Pellkofer et al., 2013). Patients with more severe pain have decreased functionality in SF-36 components of physical health and energy/fatigue. Low pain is associated with better quality of life function, whereas moderate and severe pain appear to equally impact functioning. Likewise, those in the low pain severity category endorse better anxiety and sleep outcomes among patients with NMOSD, whereas moderate and severe pain appear to equally affect these outcomes, as measured by Neuro-QoL. This suggests that both moderate and severe pain are equally impactful on QoL and co-occurring symptoms. Reducing pain may contribute to the treatment of other co-occurring symptoms, including anxiety, depression and sleep disturbance. As depression in the NMOSD population is under-recognized and undertreated with higher

levels of suicidality (Chavarro, et al., 2016), addressing pain in these patients may enable better emotional wellbeing functioning.

This is the first study to compare the amount of depression, anxiety and sleep disturbances in patients with NMOSD to normative data and found no differences. This interesting finding in a population that experiences persistent pain may suggest remarkable resiliency, particularly when coupled with the finding that mental and social functioning was not significantly impacted by pain within patients with NMOSD. Because some patients were recruited through an online social media support group, self-perceptions of functionality may be influenced by access to communal support in this rare disease and may contribute to enhanced resiliency. While the current study cannot address this finding, it deserves further exploration in future analyses of patients with NMOSD, particularly given that other research in NMOSD has reported a reduction in mental and social functioning due to pain (Zhao et al., 2014).

Collectively, our results implicate pain as a possible to many components that interfere with QoL, as characterized by declines in physical and general health. Supporting this contention is the finding that quality of life significantly differs in patients with NMOSD based on their pain severity. These data add to the body of evidence that pain may be the *primary* driver of many components that collectively contribute to poor QoL in patients with NMOSD, though longitudinal studies are needed to confirm this. It is worth noting that pain severity correlates highly with pain interference. This is important since pain severity can be quickly captured in the course of a busy clinic day, but it is only of value if it appropriately reflects how pain is affecting a patient on a daily basis outside of the clinic. This study suggests that acquiring a simple NRS pain score may act as a reliable surrogate of overall QoL in NMOSD patients.

There are three important limitations to this study worth noting. First was the inability to collect disability data. Because not all patients were seen in person, a disability score could not be ascertained uniformly across all participants. As disability accumulates in NMOSD with each attack, delay in diagnosis and delay in initiation of preventive therapy has been shown to act as a surrogate for disability in patients with NMOSD (Mealy et al., 2018). While there was no difference in diagnostic delay across pain severity categories, a more direct capture of disability would be beneficial in future investigations. A second limitation regards the sample evaluated. While all patients seen at the Johns Hopkins NMO Clinic or who belong to the social media support group were invited for inclusion into this study, participation bias may influence those who chose to participate, thus affecting the representativeness of the NMOSD population as a whole. Lastly, while the cross-sectional study design enabled data collection in a relatively large number of patients for this rare disease, it does not define the direction of relationships. While other disease states report a bidirectional relationship (Amtmann et al., 2015), it is yet unknown whether patients with increased anxiety and/or poor sleep quality are more likely to report higher levels of pain, or whether pain severity increases anxiety and sleep disruption in this population. A comprehensive longitudinal investigation into the degree of change in co-occurring symptoms reported by patients in response to a pain intervention may be necessary to further clarify the complexity of these relationships in patients with NMOSD.

References

Amtmann, D., Askew, R. L., Kim, J., Chung, H., Ehde, D. M., Bombardier, C. H., . . . Johnson, K. L. (2015). Pain affects depression through anxiety, fatigue, and sleep in multiple sclerosis. *Rehabilitation Psychology, 60*(1), 81-90. doi:10.1037/rep0000027 [doi]

Cella, D., Nowinski, C., Peterman, A., Victorson, D., Miller, D., Lai, J. S., & Moy, C. (2011). The neurology quality-of-life measurement initiative. *Archives of Physical Medicine and Rehabilitation, 92*(10 Suppl), S28-36. doi:10.1016/j.apmr.2011.01.025 [doi]

Chavarro, V. S., Mealy, M. A., Simpson, A., Lacheta, A., Pache, F., Ruprecht, K., . . . Levy, M. (2016). Insufficient treatment of severe depression in neuromyelitis optica spectrum disorder. *Neurology(R) Neuroimmunology & Neuroinflammation, 3*(6), e286. doi:10.1212/NXI.0000000000000286 [doi]

Cleeland, C. S. The Brief Pain Inventory User Guide. (2009). Available from https://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf. Accessed June 23, 2016.

Kanamori, Y., Nakashima, I., Takai, Y., Nishiyama, S., Kuroda, H., Takahashi, T., . . . Itoyama, Y. (2011). Pain in neuromyelitis optica and its effect on quality of life: A cross-sectional study. *Neurology, 77*(7), 652-658. doi:10.1212/WNL.0b013e318229e694 [doi]

Kim, H. J., Abraham, I., & Malone, P. S. (2013). Analytical methods and issues for symptom cluster research in oncology. *Current Opinion in Supportive and Palliative Care, 7*(1), 45-53. doi:10.1097/SPC.0b013e32835bf28b [doi]

Kong, Y., Okoruwa, H., Revis, J., Tackley, G., Leite, M. I., Lee, M., . . . Palace, J. (2016). Pain in patients with transverse myelitis and its relationship to aquaporin 4 antibody status. *Journal of the Neurological Sciences, 368*, 84-88. doi:10.1016/j.jns.2016.06.041 [doi]

McHorney, C. A., Ware, J. E.,Jr, Lu, J. F., & Sherbourne, C. D. (1994). The MOS 36-item short-form health survey (SF-36): III. tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care, 32*(1), 40-66.

Mealy, M. A., Kessler, R. A., Rimler, Z., Reid, A., Totonis, L., Cutter, G., . . . Levy, M. (2018). Mortality in neuromyelitis optica is strongly associated with african ancestry. *Neurology(R) Neuroimmunology & Neuroinflammation, 5*(4), e468. doi:10.1212/NXI.0000000000000468 [doi]

Mealy, M. A., Boscoe, A., Caro, J., Levy, M. (2018). Assessment of Patients with Neuromyelitis Optica Spectrum Disorder Using EQ-5D. *Int J MS Care.* Online ahead of print: doi.org/10.7224/1537-2073.2017-076.

Mutch, K., Methley, A., Moore, P., & Jacob, A. (2014). Life on hold: The experience of living with neuromyelitis optica. *Disability and Rehabilitation, 36*(13), 1100-1107. doi:10.3109/09638288.2013.833301 [doi]

NINDS User Manual Neuro-QoL. (2015). Available from http://www.healthmeasures.net/images/neuro_qol/Neuro-QOL_User_Manual_v2_24Mar2015.pdf. Accessed March 31, 2019.

Pellkofer, H. L., Havla, J., Hauer, D., Schelling, G., Azad, S. C., Kuempfel, T., . . . Huge, V. (2013). The major brain endocannabinoid 2-AG controls neuropathic pain and mechanical hyperalgesia in patients with neuromyelitis optica. *PloS One, 8*(8), e71500. doi:10.1371/journal.pone.0071500 [doi]

Qian, P., Lancia, S., Alvarez, E., Klawiter, E. C., Cross, A. H., & Naismith, R. T. (2012). Association of neuromyelitis optica with severe and intractable pain. *Archives of Neurology, 69*(11), 1482-1487. doi:1355367 [pii]

Ware, J. E. (1994). SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, New England Medical Center Hospitals.

Ware, J. E., Snow, K. K., Kosinski, M., & Gandek, B. (1994). SF-36 Health Survey: Manual and Interpretation Guide. Boston, MA: The Health Institute, New England Medical Center Hospitals.

Wingerchuk, D. M., Banwell, B., Bennett, J. L., Cabre, P., Carroll, W., Chitnis, T., . . . International Panel for NMO Diagnosis. (2015). International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology, 85*(2), 177-189. doi:10.1212/WNL.0000000000001729

Table 1: Demographic and clinical characteristics of participants

	Low pain severity (0-2)	Moderate pain severity (3-6)	High pain severity (7-10)	*p*-value
Participants (*n*=72)	22	23	27	N/A
Female sex	20 (91%)	21 (91%)	24 (89%)	0.95
Race				
Caucasian American	17 (77%)	19 (83%)	14 (52%)	0.16
African American	4 (18%)	3 (13%)	11 (41%)	
Other	1 (5%)	1 (4%)	2 (7%)	
Age				
Median (IQR)	57.3 (10.1)	49.1 (16.2)	57.6 (20.3)	0.14
Mean (SD)	55.9 (10.7)	50.0 (12.0)	57.7 (11.3)	
Disease duration (years)				
Median (IQR)	5.8 (7.5)	5.0 (5.3)	8.3 (12.0)	0.31
Mean (SD)	9.7 (8.2)	8.3 (8.6)	11.2 (8.9)	
Delay in diagnosis (years)				
Median (IQR)	0.6 (2.6)	0.3 (1.0)	0.6 (5.3)	0.06
Mean (SD)	3.7 (6.6)	2.4 (6.4)	3.8 (5.8)	
AQP4 seropositive	18 (82%)	20 (87%)	27 (100%)	0.13
History of myelitis	18 (82%)	21 (91%)	26 (96%)	0.23

Table 2: Effect of pain severity category on health-related QoL, measured by SF-36 sub-scales

	Low pain (0-2)	Moderate pain (3-6)	High pain (7-10)	*p*-value
Physical function				
Median (IQR)	80.0 (60.0)	65.0 (60.0)	20.0 (60.0)	0.010
Mean (SD)	63.6 (34.4)	56.1 (30.5)	36.1 (32.9)	
Physical role limitations				
Median (IQR)	50.0 (75.0)	25 (50.0)	0 (50.0)	0.008
Mean (SD)	53.4 (40.0)	28.3 (35.6)	21.3 (31.5)	
Pain				
Median (IQR)	80.0 (22.5)	57.5 (22.5)	45.0 (25.0)	0.0005
Mean (SD)	73.4 (27.4)	55.7 (20.7)	46.0 (22.6)	
Emotional role limitations				
Mean (SD)	72.7 (39.4)	56.5 (44.3)	48.1 (39.6)	0.087
Median (IQR)	100 (66.7)	66.7 (100)	33.3 (100)	
Emotional wellbeing				
Median (IQR)	45.0 (15.0)	50.0 (20.0)	45.0 (10.0)	0.286
Mean (SD)	43.9 (11.2)	48.0 (10.4)	48.0 (8.9)	
Social function				
Median (IQR)	100 (37.5)	75.0 (37.5)	75.0 (25.0)	0.061
Mean (SD)	82.4 (25.5)	70.1 (23.5)	69.9 (26.2)	
Energy/fatigue				
Median (IQR)	52.0 (25.0)	40.0 (10.0)	40.0 (15.0)	0.008
Mean (SD)	50.9 (14.4)	42.2 (12.7)	39.1 (10.3)	
General health				
Mean (SD)	52.7 (24.3)	41.3 (15.6)	38.5 (16.1)	0.058
Median (IQR)	52.5 (40.0)	45.0 (20.0)	35.0 (25.0)	

Table 3: Effect of pain severity category on co-occurring symptoms, measured by Neuro-QoL anxiety, depression, sleep disturbance scales, and BPI pain interference

	Low (0-2)	Moderate (3-6)	High (7-10)	*p*-value
Anxiety				
Median (IQR)	41.6 (8.8)	50.4 (14.1)	50.4 (14.1)	0.050
Mean (SD)	46.3 (5.6)	51.0 (8.1)	51.4 (8.2)	
Depression				
Median (IQR)	46.4 (7.9)	50.1 (8.4)	50.6 (9.9)	0.115
Mean (SD)	47.5 (8.1)	48.7 (5.4)	50.9 (6.8)	
Sleep disturbance				
Median (IQR)	49.0 (8.8)	57.7 (7.4)	56.5 (12.8)	0.001
Mean (SD)	49.2 (7.0)	57.5 (8.1)	56.8 (9.3)	
Pain interference				
Median (IQR)	0.2 (0.7)	4.3 (2.8)	6.1 (2.3)	<0.0001
Mean (SD)	0.7 (1.3)	4.0 (2.1)	5.8 (1.8)	

Table 4: Comparing Neuro-QoL anxiety, depression, sleep disturbance scales in patients with NMOSD to normative U.S. data

	NMOSD	US norms	*p*-value	95% CI
Anxiety Mean (SD)	50.9 (34.3)	50 (10)	0.8	-21.0, 1.6
Depression Mean (SD)	49.2 (6.9)	50 (10)	0.5	-2.5, 0.9
Sleep interference Mean (SD)	54.6 (25.9)	50 (10)	0.5	-3.0, 1.4

Chapter 5: Synthesis/Discussion

The studies herein examined pain in patients with neuromyelitis optica spectrum disorder (NMOSD). Specifically, we investigated the use of Scrambler therapy for treatment of central neuropathic pain and explored whether reducing pain in this population could improve co-occurring symptoms and quality of life (QoL). Given the interrelatedness of symptoms, as outlined by the Theory of Unpleasant Symptoms (TOUS; Lenz et al., 1997), pain reduction and improvement in co-occurring symptoms may have a clinically meaningful impact to patients' physical, social and emotional functioning.

Pain has been shown to interfere with QoL and may be the best independent predictor of poor QoL in NMOSD (Kong et al., 2016; Mealy et al., 2018). Central neuropathic pain (CNP) is particularly severe, pervasive and intractable to available treatments (Zhao et al., 2014). This is the first interventional pain trial in the United States to be conducted in patients with NMOSD, and the first to announce results worldwide. It is also the first trial to examine Scrambler use in patients with CNP. Results from this study may guide health care providers with non-pharmacologic approaches for comprehensive symptom management in this population. Furthermore, while treatment of severe pain was a particular unmet need in the NMOSD patient population, the knowledge gained from this investigation may be applicable to other more common conditions that cause CNP, including multiple sclerosis, spinal cord injury and stroke.

Summary of Findings

Two studies were conducted in parallel. The synthesis of results from these will help to implement a well-informed Phase III randomized sham-controlled trial where the results are more likely to decrease pain in patients with NMOSD. Importantly, the data captured suggests

that reduction in pain will meaningfully impact the quality of lives in the target population. Targeting pain without considering the effect on QoL may yield a statistically significant reduction in pain without translating into enhanced QoL. This is especially true in light of chronic disease research that suggests that improving a single symptom in diseases where other symptoms are common without considering these co-occurring symptoms may not impact QoL (Kim et al., 2013). As such, the rationale for this two-pronged approach was to gain insights for future studies that are more likely to yield clinically meaningful results.

The first two aims of the dissertation utilized a cohort of 22 patients with NMOSD who have CNP and were recruited from the Johns Hopkins NMOSD Clinic. Patients were randomized 1:1 and blinded to undergo either Scrambler or sham therapy daily for 10 consecutive weekdays.

Aim 1

The goal of Aim 1 was to investigate the effectiveness, safety, acceptability and feasibility of Scrambler therapy when compared to sham.

Sub-aim 1. Feasibility and acceptability were measured based on response to a brief patient survey presented to patients following treatment, as follows, comparing Scrambler-treated patients to those in the sham arm: “Do you think you received treatment?” (Yes/No), and “Would you want to continue treatment in clinic, if available?” (Yes/No). Feasibility was further measured based on patient adherence to the study visit schedule, comparing those in the Scrambler arm to the sham arm. Results from this aim found no difference between groups in patients who thought they received treatment, as well as no difference in whether they would want to continue such treatment. Most patients completed all treatments, with no difference found between arms.

Sub-aim 2. Safety of the intervention was evaluated by comparing Adverse Events (AEs) and Serious Adverse Events (SAEs) in the treated versus sham groups. Safety profiles were similar between the Scrambler-treated arm and the sham arm, with one participant in the sham arm experiencing SAEs related to infections during the follow-up period. Pain did not increase in either group.

Sub-aim 3. Effectiveness of Scrambler therapy was evaluated by comparing change in numeric rating scale (NRS) pain scores from baseline to end of treatment between the Scrambler treated and sham arms. The median baseline NRS pain score decreased from 5.0 to 1.5 following 10 days of treatment with Scrambler therapy, whereas the median NRS score did not significantly decrease in the sham arm. This effect was sustained at 30 days following treatment, though not at 60 days.

Aim 2

The goal of Aim 2 was to explore the effect of Scrambler therapy on co-occurring symptoms, including pain interference, anxiety, depression and sleep disturbances, comparing patients in the Scrambler-treated arm to those in the sham arm. Prior to initiation of Scrambler therapy, patients were asked to complete each of the following measurement tools to determine baseline pain severity and interference, anxiety, depression, and sleep disturbance, respectively: Brief Pain Inventory (BPI), Neuro-QoL [Quality of Life in Neurological Disorders] Short Form v1.0 - Anxiety, Neuro-QoL Short Form v1.0 - Depression, and Neuro-QoL Short Form v1.0 - Sleep Disturbance (Cleeland, 2009; Cella et al., 2007). Non-parametric testing revealed that depression scores were reduced from baseline in the Scrambler-treated group only. A subanalysis that only considered patients who responded to treatment found a decline from baseline in

anxiety in Scrambler-treated patients as well. Symptoms were unchanged in patients receiving sham treatment.

In parallel with this aim, a third aim of this dissertation involved a cross-sectional investigation in 72 patients diagnosed with NMOSD who were recruited via convenience sampling through the Johns Hopkins NMO Clinic and an online social media patient support group. This included data from the 22 patients in the Scrambler study at their baseline timepoint.

Aim 3

The goal of Aim 3 was to assess the impact of pain on other symptoms that co-occur in patients with NMOSD, including anxiety, depression and sleep disturbance, as well as QoL. Patients accessed Brief Pain Inventory (BPI; Cleeland, 2009), Neuro-QoL [Quality of Life in Neurological Disorders] Short Form v1.0 - Anxiety, Neuro-QoL Short Form v1.0 - Depression, Neuro-QoL Short Form v1.0 - Sleep Disturbance (Cella et al., 2007) and Short Form-36 Health Inventory (SF-36; Ware et al., 1994) via a secure online portal. While on average patients with NMOSD do not have higher amounts of depression, anxiety or sleep disturbance compared with available normative data, our data revealed that patients with moderate and high pain severity were more likely to endorse lower functioning and higher anxiety and sleep disturbance than those patients with low or no pain.

Discussion

Strengths and Limitations

This study was innovative in three crucial ways, as discussed below:

1. It addressed the important and severe problem of pain in an undertreated population.

2. It provided proof-of-concept for treatment of CNP that may be applicable to other etiologies, in addition to NMOSD.
3. It added to the body of knowledge for conducting sham-controlled studies using Scrambler therapy.

Although NMOSD is a rare disease, it is devastating for those who have it. The pain experienced by this population of patients is particularly refractory to available treatments (Qian et al., 2012). Nonetheless, no interventional trials that target pain have been conducted in patients with NMOSD. The most significant strength of this study is that it addresses the high unmet need of these patients. The controlled study design used to determine efficacy of Scrambler therapy allows for specific questions to be answered which will guide future research. Because Scrambler therapy has never been rigorously tested for CNP treatment, it would have been impractical to test its use in a larger trial without first ascertaining if it is a feasible, safe and potentially effective option. We also conducted a parallel study to provide additional context to the basis of targeting pain to improve QoL in NMOSD. In a larger cohort of NMOSD, we assessed cross-sectional evidence that pain severity impacts components of quality of life, the purpose of which was to explore if pain severity may contribute to components that lead to poor QoL in patients with NMOSD. The results of these innovative studies provide a strong foundation of evidence to support further investigation of Scrambler therapy use for NMOSD, as well as other etiologies of CNP.

Published evidence for the use of Scrambler therapy is limited. Most research thus far involved open label, observational studies (Majithia et al., 2016). Only two previously reported studies utilized a blinded, randomized sham-controlled design (Campbell et al., 2013; Starkweather et al., 2015). Assessing the feasibility of the sham procedure further informs a

larger trial. The current study provides deeper insight into a pragmatic way to provide patients with sham intervention, through which patients reported being adequately masked. The sham protocol used in this investigation can be adapted for use in any randomized Scrambler trial, regardless of the population being studied.

This study is not without its limitations. Due to inadequate resources, a third party could not be recruited to receive training in and provide Scrambler therapy for this trial. As such, the primary investigator served as the Scrambler technician, and was therefore unblinded. To mitigate the risk associated with a single-blinded study design, patient-reported outcomes data were collected by an independent study coordinator. To further promote study integrity, randomization was additionally performed by an independent party. In the future, the data from the current study may provide sufficient evidence to facilitate the procurement of resources that will enhance the scientific rigor of a larger Phase III trial.

Secondly, the Scrambler component of this dissertation was powered for effect at the end of the 10-day treatment based on peripheral neuropathy data. While it was encouraging to find that this allowed for an adequately powered study to detect a difference between the Scrambler treated and sham arms at this time point, the practicality of using Scrambler increases if the effect is sustained. In this study, the effect was sustained at the 30-day time point, but not at the 60-day time point. Re-emergence of pain has been described in open-label, observational studies, in treatment of both peripheral and central pain conditions (Smith et al., 2017; Mealy et al., in press). Data suggest that pain continues to be amenable to subsequent treatment, often with fewer Scrambler treatment sessions needed (Smith et al., 2017). Nonetheless, powering a larger Phase III study with a primary endpoint for effect at 60 days rather than at end of treatment would increase the study rigor, practicality and appeal of Scrambler treatment. A post hoc calculation

was conducted to determine how to power a Phase III trial with this change in primary outcome and indicated that 29 patients per arm would be sufficient to show such an effect.

Implications for Nursing

A primary purpose of nursing research is to provide evidence-based research that promotes quality health outcomes for patients. Despite being one of the most common medical complaints, pain is often unrelieved and undertreated (McCarberg, Nicholson, Todd, Palmer, & Penles, 2008). With its physical, psychological, and economic impact, it is well-documented that pain affects QoL. Alleviating suffering and enhancing QoL is in direct alignment with nursing research. As such, the implications of the current study for nursing research are clear.

The current study was informed by TOUS (Lenz et al., 1997), which postulates that co-occurring symptoms are both influenced by and influence physiologic, psychologic, and situational factors, and that the interaction among these factors impacts performance. The discovery that patients who report moderate to severe pain were more likely to endorse lower functioning, more anxiety and more sleep disturbance supports the underpinning of this theory. This adds credence to the practicality of this model for use in nursing research that involves symptom co-occurrence and helps to refine its application. Although only pain was directly intervened on, the indication that there are indirect effects on other symptoms may make this intervention more clinically meaningful to patients. This concept is supported by research involving activation of the HPA axis, which shows that pain results in increased cortisol levels, which is associated with mood disorders (Gerrits et al. 2014). Improving functional status and QoL may afford patients with opportunities to engage in richer lives socially, personally and professionally in the context of significant pain reduction, and Scrambler may enable that in a non-invasive way. To date, medical research in NMOSD has primarily focused on disease

suppression and cure. Nursing research provides the unique opportunity to advocate for patients by recognizing the impact symptoms have on QoL and exploring remediation.

From a practical standpoint, the suggestion based on these data that a simple numeric rating of pain may act as an adequate surrogate of pain interference and components of QoL is a valuable finding that merits further validation. This can be easily captured by health care providers, even in the course of a busy day, but is only of value if targeting this number might translate into a clinically meaningful change in the function of patients with NMOSD.

Recommendations for Future Research

The primary focus of this dissertation was to capture data that can inform a larger trial toward the effort of alleviating pain in this severely affected population. The data obtained from this study establish an exciting foundation for future evaluation of Scrambler use in this population. The evidence suggests that 1) targeting pain may impact QoL, and 2) Scrambler therapy is an effective and safe non-invasive treatment for pain in patients with NMOSD. As such, a Phase III trial that is better powered to address sustainability of treatment and effect on co-occurring symptoms and QoL over time is warranted, particularly given that effects on sleep may emerge due to activation of the HPA axis, but may be delayed. Because of the subjectivity of patient-reported outcomes, such a study would benefit from combining patient-reported outcomes with objective measures such as changes in serum and salivary biomarkers of inflammation and pain in response to Scrambler therapy. Lastly, a larger trial would provide an opportunity to implement a study design that clarifies how to protocolize treatment of re-emergence of pain with subsequent treatments for sustained effect. Because of the rarity of the diagnosis, engaging multiple sites for patient recruitment in a larger trial may be warranted.

Given that response can vary based on the technician delivering treatment (Moon et al., 2015), it would be important to implement systematic and consistent training across all sites.

Another area of future research could be aimed at instrument development specific to this population, as well as validation of instruments that currently exist. At this time, no instruments have been developed and/or validated for use in patients with NMOSD. Because the symptoms themselves, as well as the psychosocial impact of these symptoms on QoL, are unique to any disease, ensuring that instruments adequately capture the patient experience is necessary.

Lastly, this research suggests that patients with NMOSD are no more anxious or depressed than general U.S. populations. This suggests that these patients display remarkable resiliency despite being faced with terrible disability and uncertain futures. Developing a deeper understanding of whether this signal of resiliency is accurate and what contributes to this resiliency would be an interesting topic for future research. Given that NMOSD is a rare disease, there tends to be an active community of patients who are involved in advocacy groups and online support groups. Recruitment for Aim 3 involved soliciting patients in such a group, though only 12 of the 72 were recruited from this source. Nonetheless, many others who were recruited through the Hopkins NMO Clinic are also involved in such organizations. Investigating how engagement with these types of resources impacts symptoms and QoL would be of future interest.

References

Alschuler, K. N., Jensen, M. P., & Ehde, D. M. (2012). The association of depression with pain-related treatment utilization in patients with multiple sclerosis. *Pain Medicine (Malden, Mass.), 13*(12), 1648-1657. doi:10.1111/j.1526-4637.2012.01513.x [doi]

Amtmann, D., Askew, R. L., Kim, J., Chung, H., Ehde, D. M., Bombardier, C. H., . . . Johnson, K. L. (2015). Pain affects depression through anxiety, fatigue, and sleep in multiple sclerosis. *Rehabilitation Psychology, 60*(1), 81-90. doi:10.1037/rep0000027 [doi]

Araki, M., Matsuoka, T., Miyamoto, K., Kusunoki, S., Okamoto, T., Murata, M., . . . Yamamura, T. (2014). Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: A pilot study. *Neurology, 82*(15), 1302-1306. doi:10.1212/WNL.0000000000000317 [doi]

Archibald, C. J., McGrath, P. J., Ritvo, P. G., Fisk, J. D., Bhan, V., Maxner, C. E., & Murray, T. J. (1994). Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients. *Pain, 58*(1), 89-93. doi:0304-3959(94)90188-0 [pii]

Bernardes, S. F., Keogh, E., & Lima, M. L. (2008). Bridging the gap between pain and gender research: A selective literature review. *European Journal of Pain (London, England), 12*(4), 427-440. doi:S1090-3801(07)00646-5 [pii]

Blivis, D., Haspel, G., Mannes, P. Z., O'Donovan, M. J., & Iadarola, M. J. (2017). Identification of a novel spinal nociceptive-motor gate control for adelta pain stimuli in rats. *Elife, 6*, 10.7554/eLife.23584. doi:10.7554/eLife.23584 [doi]

Boldt, I., Eriks-Hoogland, I., Brinkhof, M. W., de Bie, R., Joggi, D., & von Elm, E. (2014). Non-pharmacological interventions for chronic pain in people with spinal cord injury. *The Cochrane Database of Systematic Reviews, 11*, CD009177. doi:10.1002/14651858.CD009177.pub2 [doi]

Borsook, D. (2012). Neurological diseases and pain. *Brain : A Journal of Neurology, 135*(Pt 2), 320-344. doi:10.1093/brain/awr271 [doi]

Bradl, M., Kanamori, Y., Nakashima, I., Misu, T., Fujihara, K., Lassmann, H., & Sandkuhler, J. (2014). Pain in neuromyelitis optica--prevalence, pathogenesis and therapy. *Nature Reviews.Neurology, 10*(9), 529-536. doi:10.1038/nrneurol.2014.129 [doi]

Breivik, H., Borchgrevink, P. C., Allen, S. M., Rosseland, L. A., Romundstad, L., Hals, E. K., . . . Stubhaug, A. (2008). Assessment of pain. *British Journal of Anaesthesia, 101*(1), 17-24. doi:10.1093/bja/aen103 [doi]

Bryce, T. N., Biering-Sorensen, F., Finnerup, N. B., Cardenas, D. D., Defrin, R., Ivan, E., . . . Dijkers, M. (2012). International spinal cord injury pain (ISCIP) classification: Part 2. initial validation using vignettes. *Spinal Cord, 50*(6), 404-412. doi:10.1038/sc.2012.2 [doi]

Calmare Technologies, Inc. Calmare Model MC-5A Non-Invasive Pain Therapy Treatment User's Manual. 2008. Available from http://calmarett.com/media/pdf/User%20Manual_International%20Version_25Nov2008.pdf . Accessed September 6, 2016.

Campbell, T., Nimunkar, A.J., Eickhoff, J.C., Backonja, M., Cleary, J.F.… Yen TY. (2013). A randomized, double-blind study of "Scrambler" therapy versus sham for painful chemotherapy-induced peripheral neuropathy. J Clin Oncol. 31:suppl; abstr 9635.

Cella, D., Nowinski, C., Peterman, A., Victorson, D., Miller, D., Lai, J. S., & Moy, C. (2011). The neurology quality-of-life measurement initiative. Archives of Physical Medicine and Rehabilitation, 92(10 Suppl), S28-36. doi:10.1016/j.apmr.2011.01.025 [doi]

Cella, D., Wagner, L., Cashy, J., Hensing, T. A., Yount, S., & Lilenbaum, R. C. (2007). Should health-related quality of life be measured in cancer symptom management clinical trials? lessons learned using the functional assessment of cancer therapy. Journal of the National Cancer Institute.Monographs, (37):53-60. doi(37), 53-60. doi:2007/37/53 [pii]

Centonze, D. (2014). Advances in the management of multiple sclerosis spasticity: Multiple sclerosis spasticity nervous pathways. *European Neurology, 72 Suppl 1*, 6-8. doi:10.1159/000367615 [doi]

Chavarro, V. S., Mealy, M. A., Simpson, A., Lacheta, A., Pache, F., Ruprecht, K., . . . Levy, M. (2016). Insufficient treatment of severe depression in neuromyelitis optica spectrum disorder. *Neurology(R) Neuroimmunology & Neuroinflammation, 3*(6), e286. doi:10.1212/NXI.0000000000000286 [doi]

Cleeland, C. S. The Brief Pain Inventory User Guide. (2009). Available from https://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf. Accessed June 23, 2016.

Cleeland, C. S., Gonin, R., Hatfield, A. K., Edmonson, J. H., Blum, R. H., Stewart, J. A., & Pandya, K. J. (1994). Pain and its treatment in outpatients with metastatic cancer. *The New England Journal of Medicine, 330*(9), 592-596. doi:10.1056/NEJM199403033300902 [doi]

Cohen, S. P., & Mao, J. (2014). Neuropathic pain: Mechanisms and their clinical implications. *BMJ (Clinical Research Ed.), 348*, f7656. doi:10.1136/bmj.f7656 [doi]

Coplan, P. M., Schmader, K., Nikas, A., Chan, I. S., Choo, P., Levin, M. J., . . . Oxman, M. N. (2004). Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: Adaptation of the brief pain inventory. *The Journal of Pain : Official Journal of the American Pain Society, 5*(6), 344-356. doi:S1526590004008272 [pii]

Coyne, P. J., Wan, W., Dodson, P., Swainey, C., & Smith, T. J. (2013). A trial of scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. *Journal of Pain & Palliative Care Pharmacotherapy, 27*(4), 359-364. doi:10.3109/15360288.2013.847519 [doi]

Crayton, H. J., & Rossman, H. S. (2006). Managing the symptoms of multiple sclerosis: A multimodal approach. *Clinical Therapeutics, 28*(4), 445-460. doi:S0149-2918(06)00093-2 [pii]

D'Amato, S. J., Mealy, M. A., Erdek, M. A., Kozachik, S., & Smith, T. J. (2018). Scrambler therapy for the treatment of chronic central pain: A case report. *A&A Practice, 10*(12), 313-315. doi:10.1213/XAA.0000000000000695 [doi]

Daut, R. L., Cleeland, C. S., & Flanery, R. C. (1983). Development of the wisconsin brief pain questionnaire to assess pain in cancer and other diseases. *Pain, 17*(2), 197-210. doi:0304-3959(83)90143-4 [pii]

Definition of classes of evidence (CoE) and overall strength of evidence (SoE). (2014). *Evidence-Based Spine-Care Journal, 5*(1), 71-0034-1373841. doi:10.1055/s-0034-1373841 [doi]

Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T., . . . Zavisic, S. (2008). Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *The Journal of Pain : Official Journal of the American Pain Society, 9*(2), 105-121. doi:S1526-5900(07)00899-1 [pii]

Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T., . . . Zavisic, S. (2008). Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *The Journal of Pain : Official Journal of the American Pain Society, 9*(2), 105-121. doi:S1526-5900(07)00899-1 [pii]

Ehde, D. M., Nitsch, K. P., & Smiley, J. P. (2015). Measurement characteristics and clinical utility of the brief pain inventory-short form for individuals with multiple sclerosis. *Rehabilitation Psychology, 60*(4), 365-366. doi:10.1037/rep0000065 [doi]

Erdemoglu, A. K., & Koc, R. (2013). Brief pain inventory score identifying and discriminating neuropathic and nociceptive pain. *Acta Neurologica Scandinavica, 128*(5), 351-358. doi:10.1111/ane.12131 [doi]

Finnerup, N. B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R. H., . . . Wallace, M. (2015). Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *The Lancet.Neurology, 14*(2), 162-173. doi:10.1016/S1474-4422(14)70251-0 [doi]

Food and Drug Administration. 501(k) Summary for the Competative Technologies, Inc. Scrambler Therapy MC-5A TENS Device. (2009). https://www.accessdata.fda.gov/cdrh_docs/pdf8/K081255.pdf. Accessed 10/14/2016.

Franneby, U., Gunnarsson, U., Andersson, M., Heuman, R., Nordin, P., Nyren, O., & Sandblom, G. (2008). Validation of an inguinal pain questionnaire for assessment of chronic pain after groin hernia repair. *The British Journal of Surgery, 95*(4), 488-493. doi:10.1002/bjs.6014 [doi]

Garrison, D. W., & Foreman, R. D. (1994). Decreased activity of spontaneous and noxiously evoked dorsal horn cells during transcutaneous electrical nerve stimulation (TENS). *Pain, 58*(3), 309-315.

Gerrits, M. J., van Oppen, P., Leone, S. S., van Marwijk, H. W. J., van der Horst, H. E., Penninx, B. W. (2014). Pain, not chronic disease, is associated with the recurrence of depressive and anxiety disorders. 14:187.

Gonzalez, H., Sunnerhagen, K. S., Sjoberg, I., Kaponides, G., Olsson, T., & Borg, K. (2006). Intravenous immunoglobulin for post-polio syndrome: A randomised controlled trial. *The Lancet.Neurology, 5*(6), 493-500. doi:S1474-4422(06)70447-1 [pii]

Han, Z. A., Song, D. H., Oh, H. M., & Chung, M. E. (2016). Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. *Annals of Neurology, 79*(4), 569-578. doi:10.1002/ana.24605 [doi]

Hanley MA, Jensen MP, Ehde DM, Robinson LR, Cardenas DD, Turner JA, Smith DG. (2006). Clinically significant change in pain intensity ratings in persons with spinal cord injury or amputation. Clin J Pain, *22*(1):25-31.

Heutink, M., Post, M. W., Bongers-Janssen, H. M., Dijkstra, C. A., Snoek, G. J., Spijkerman, D. C., & Lindeman, E. (2012). The CONECSI trial: Results of a randomized controlled trial of a multidisciplinary cognitive behavioral program for coping with chronic neuropathic pain after spinal cord injury. *Pain, 153*(1), 120-128. doi:10.1016/j.pain.2011.09.029 [doi]

Heutink, M., Post, M. W., Luthart, P., Schuitemaker, M., Slangen, S., Sweers, J., . . . Lindeman, E. (2014). Long-term outcomes of a multidisciplinary cognitive behavioural programme for coping with chronic neuropathic spinal cord injury pain. *Journal of Rehabilitation Medicine, 46*(6), 540-545. doi:10.2340/16501977-1798 [doi]

Hollinger, K. R., Franke, C., Arenivas, A., Woods, S. R., Mealy, M. A., Levy, M., & Kaplin, A. I. (2016). Cognition, mood, and purpose in life in neuromyelitis optica spectrum disorder. *Journal of the Neurological Sciences, 362*, 85-90. doi:10.1016/j.jns.2016.01.010 [doi]

Huang, Q., Wang, J., Zhou, Y., Yang, H., Wang, Z., Yan, Z., . . . Qiu, W. (2018). Low-dose mycophenolate mofetil for treatment of neuromyelitis optica spectrum disorders: A prospective multicenter study in south china. *Frontiers in Immunology, 9*, 2066. doi:10.3389/fimmu.2018.02066 [doi]

Jarius, S., Ruprecht, K., Wildemann, B., Kuempfel, T., Ringelstein, M., Geis, C., . . . Paul, F. (2012). Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients. *Journal of Neuroinflammation, 9*, 14-2094-9-14. doi:10.1186/1742-2094-9-14 [doi]

Joo, S. Y., Cho, Y. S., Cho, S. R., Kym, D., & Seo, C. H. (2017). Effects of pain scrambler therapy for management of burn scar pruritus: A pilot study. *Burns : Journal of the International Society for Burn Injuries, 43*(3), 514-519. doi:S0305-4179(16)30409-0 [pii]

Kanamori, Y., Nakashima, I., Takai, Y., Nishiyama, S., Kuroda, H., Takahashi, T., . . . Itoyama, Y. (2011). Pain in neuromyelitis optica and its effect on quality of life: A cross-sectional study. *Neurology, 77*(7), 652-658. doi:10.1212/WNL.0b013e318229e694 [doi]

Kapstad, H., Hanestad, B. R., Langeland, N., Rustoen, T., & Stavem, K. (2008). Cutpoints for mild, moderate and severe pain in patients with osteoarthritis of the hip or knee ready for joint replacement surgery. *BMC Musculoskeletal Disorders, 9*, 55-2474-9-55. doi:10.1186/1471-2474-9-55 [doi]

Kashyap, K., Joshi, S., Vig, S., Singh, V., & Bhatnagar, S. (2017). Impact of scrambler therapy on pain management and quality of life in cancer patients: A study of twenty cases. *Indian Journal of Palliative Care, 23*(1), 18-23. doi:10.4103/0973-1075.197948 [doi]

Khan, F., Amatya, B., & Kesselring, J. (2013). Longitudinal 7-year follow-up of chronic pain in persons with multiple sclerosis in the community. *Journal of Neurology, 260*(8), 2005-2015. doi:10.1007/s00415-013-6925-z [doi]

Kim, H. J., Abraham, I., & Malone, P. S. (2013). Analytical methods and issues for symptom cluster research in oncology. *Current Opinion in Supportive and Palliative Care, 7*(1), 45-53. doi:10.1097/SPC.0b013e32835bf28b [doi]

Kim, Y. N., Lee, D. K., & Lee, H. J. (2017). Effect of pain scrambler therapy on antineuralgic pain and quality of life after shingles. *Journal of Physical Therapy Science, 29*(6), 1113-1115. doi:10.1589/jpts.29.1113 [doi]

Ko, Y. K., Lee, H. Y., & Lee, W. Y. (2013). Clinical experiences on the effect of scrambler therapy for patients with postherpetic neuralgia. *The Korean Journal of Pain, 26*(1), 98-101. doi:10.3344/kjp.2013.26.1.98 [doi]

Koch-Henriksen, N., & Sørensen, P. S. (2010). The changing demographic pattern of multiple sclerosis epidemiology. *The Lancet Neurology, 9*(5), 520-532. doi:http://dx.doi.org/10.1016/S1474-4422(10)70064-8

Kong, Y., Okoruwa, H., Revis, J., Tackley, G., Leite, M. I., Lee, M., . . . Palace, J. (2016). Pain in patients with transverse myelitis and its relationship to aquaporin 4 antibody status. *Journal of the Neurological Sciences, 368*, 84-88. doi:10.1016/j.jns.2016.06.041 [doi]

Kuspinar, A., & Mayo, N. E. (2014). A review of the psychometric properties of generic utility measures in multiple sclerosis. *Pharmacoeconomics, 32*(8), 759-773. doi:10.1007/s40273-014-0167-5 [doi]

Lee, S. C., Park, K. S., Moon, J. Y., Kim, E. J., Kim, Y. C., Seo, H., . . . Lee, D. J. (2016). An exploratory study on the effectiveness of "calmare therapy" in patients with cancer-related

neuropathic pain: A pilot study. *European Journal of Oncology Nursing : The Official Journal of European Oncology Nursing Society, 21*, 1-7. doi:10.1016/j.ejon.2015.12.001 [doi]

Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: An update. *ANS.Advances in Nursing Science, 19*(3), 14-27.

Levendoglu, F., Ogun, C. O., Ozerbil, O., Ogun, T. C., & Ugurlu, H. (2004). Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine, 29*(7), 743-751. doi:00007632-200404010-00007 [pii]

Loprinzi, C. L., Le-Rademacher, J., Majithia, N., McMurray, R., Bendel, M.… Smith, T. J. (2018). Scrambler therapy for established chemotherapy-induced neuropathy: A randomized phase II trial. J Clin Oncol. 36(15): 10016-10016.

Lunn, M. P., Hughes, R. A., & Wiffen, P. J. (2014). Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *The Cochrane Database of Systematic Reviews, 1*, CD007115. doi:10.1002/14651858.CD007115.pub3 [doi]

Majithia, N., Smith, T. J., Coyne, P. J., Abdi, S., Pachman, D. R., Lachance, D., . . . Loprinzi, C. L. (2016). Scrambler therapy for the management of chronic pain. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer, 24*(6), 2807-2814. doi:10.1007/s00520-016-3177-3 [doi]

Manocchia, M., Keller, S., & Ware, J. E. (2001). Sleep problems, health-related quality of life, work functioning and health care utilization among the chronically ill. *Quality of Life*

Research : An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation, 10(4), 331-345.

Marineo, G., Iorno, V., Gandini, C., Moschini, V., & Smith, T. J. (2012). Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: Results of a pilot, randomized, controlled trial. *Journal of Pain and Symptom Management, 43*(1), 87-95. doi:10.1016/j.jpainsymman.2011.03.015 [doi]

Marrie, R. A., & Gryba, C. (2013). The incidence and prevalence of neuromyelitis optica: A systematic review. *International Journal of MS Care, 15*(3), 113-118. doi:10.7224/1537-2073.2012-048 [doi]

McCarberg, B. H., Nicholson, B. D., Todd, K. H., Palmer, T., & Penles, L. (2008). The impact of pain on quality of life and the unmet needs of pain management: Results from pain sufferers and physicians participating in an internet survey. *American Journal of Therapeutics, 15*(4), 312-320. doi:10.1097/MJT.0b013e31818164f2 [doi]

McHorney, C. A., Ware, J. E.,Jr, Lu, J. F., & Sherbourne, C. D. (1994). The MOS 36-item short-form health survey (SF-36): III. tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care, 32*(1), 40-66.

Mealy, M. A., Kessler, R. A., Rimler, Z., Reid, A., Totonis, L., Cutter, G., . . . Levy, M. (2018). Mortality in neuromyelitis optica is strongly associated with african ancestry. *Neurology(R) Neuroimmunology & Neuroinflammation, 5*(4), e468. doi:10.1212/NXI.0000000000000468 [doi]

Mealy, M. A., Wingerchuk, D. M., Greenberg, B. M., & Levy, M. (2012). Epidemiology of neuromyelitis optica in the united states: A multicenter analysis. *Archives of Neurology, 69*(9), 1176-1180. doi:10.1001/archneurol.2012.314 [doi]

Mealy, M. A., Newsome, S. D., Kozachik, S. L., Levy, M., Smith, T. J. (2018). Scrambler Therapy for Treatment-Resistant Central Neuropathic Pain in a Patient with Transverse Myelitis: A Case Report. *Int J MS Care.* In-Press. Online ahead of print: https://doi.org/10.7224/1537-2073.2017-083.

Mealy, M. A., Simpson, A., Levy, M. (2016). Comparing the Burden of Symptom Severity among Autoimmune Diseases affecting the Spinal Cord. *In 32nd European Committee for Treatment and Research in Multiple Sclerosis Annual Congress*; September 14-17; London, UK. Abstract A-777-0039-02305.

Mealy, M. A., Boscoe, A., Caro, J., Levy, M. (2018). Assessment of Patients with Neuromyelitis Optica Spectrum Disorder Using EQ-5D. *Int J MS Care.* Online ahead of print: doi.org/10.7224/1537-2073.2017-076.

Merlino, G., Fratticci, L., Lenchig, C., Valente, M., Cargnelutti, D., Picello, M., . . . Gigli, G. L. (2009). Prevalence of 'poor sleep' among patients with multiple sclerosis: An independent predictor of mental and physical status. *Sleep Medicine, 10*(1), 26-34. doi:10.1016/j.sleep.2007.11.004 [doi]

Moon, J. Y., Kurihara, C., Beckles, J. P., Williams, K. E., Jamison, D. E., & Cohen, S. P. (2015). Predictive factors associated with success and failure for calmare (scrambler) therapy: A

multicenter analysis. *The Clinical Journal of Pain, 31*(8), 750-756. doi:10.1097/AJP.0000000000000155 [doi]

Moore, P., Methley, A., Pollard, C., Mutch, K., Hamid, S., Elsone, L., & Jacob, A. (2016). Cognitive and psychiatric comorbidities in neuromyelitis optica. *Journal of the Neurological Sciences, 360*, 4-9. doi:10.1016/j.jns.2015.11.031 [doi]

Mutch, K., Methley, A., Moore, P., & Jacob, A. (2014). Life on hold: The experience of living with neuromyelitis optica. *Disability and Rehabilitation, 36*(13), 1100-1107. doi:10.3109/09638288.2013.833301 [doi]

Namjooyan, F., Ghanavati, R., Majdinasab, N., Jokari, S., & Janbozorgi, M. (2014). Uses of complementary and alternative medicine in multiple sclerosis. *Journal of Traditional and Complementary Medicine, 4*(3), 145-152. doi:10.4103/2225-4110.136543 [doi]

Newland, P. K., Naismith, R. T., & Ullione, M. (2009). The impact of pain and other symptoms on quality of life in women with relapsing-remitting multiple sclerosis. *The Journal of Neuroscience Nursing : Journal of the American Association of Neuroscience Nurses, 41*(6), 322-328.

Newland, P. K., Riley, M., Fearing, A., Neath, A., Gibson, D. (2009). Pain in women with relapsing-remitting multiple sclerosis and healthy women: Relationship to demographic variables. *MEDSURG Nursing, 19*(3), 177-182.

Nicholson Perry, K., Nicholas, M. K., Middleton, J., & Siddall, P. (2009). Psychological characteristics of people with spinal cord injury-related persisting pain referred to a tertiary

pain management center. *Journal of Rehabilitation Research and Development, 46*(1), 57-67.

Nick, S. T., Roberts, C., Billiodeaux, S., Davis, D. E., Zamanifekri, B., Sahraian, M. A., . . . Minagar, A. (2012). Multiple sclerosis and pain. *Neurological Research, 34*(9), 829-841. doi:10.1179/1743132812Y.0000000082 [doi]

NINDS User Manual Neuro-QoL. (2015). Available from http://www.healthmeasures.net/images/neuro_qol/Neuro-QOL_User_Manual_v2_24Mar2015.pdf. Accessed March 31, 2019.

Norrbrink Budh, C., Kowalski, J., & Lundeberg, T. (2006). A comprehensive pain management programme comprising educational, cognitive and behavioural interventions for neuropathic pain following spinal cord injury. *Journal of Rehabilitation Medicine, 38*(3), 172-180. doi:M1N46588657H1718 [pii]

Norrbrink, C. (2009). Transcutaneous electrical nerve stimulation for treatment of spinal cord injury neuropathic pain. *Journal of Rehabilitation Research and Development, 46*(1), 85-93.

Norrbrink, C., Lindberg, T., Wahman, K., & Bjerkefors, A. (2012). Effects of an exercise programme on musculoskeletal and neuropathic pain after spinal cord injury--results from a seated double-poling ergometer study. *Spinal Cord, 50*(6), 457-461. doi:10.1038/sc.2011.160 [doi]

Norrbrink, C., & Lundeberg, T. (2009). Tramadol in neuropathic pain after spinal cord injury: A randomized, double-blind, placebo-controlled trial. *The Clinical Journal of Pain, 25*(3), 177-184. doi:10.1097/AJP.0b013e31818a744d [doi]

Norrbrink, C., & Lundeberg, T. (2011). Acupuncture and massage therapy for neuropathic pain following spinal cord injury: An exploratory study. *Acupuncture in Medicine : Journal of the British Medical Acupuncture Society, 29*(2), 108-115. doi:10.1136/aim.2010.003269 [doi]

Notaro, P., Dell'Agnola, C. A., Dell'Agnola, A. J., Amatu, A., Bencardino, K. B., & Siena, S. (2016). Pilot evaluation of scrambler therapy for pain induced by bone and visceral metastases and refractory to standard therapies. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer, 24*(4), 1649-1654. doi:10.1007/s00520-015-2952-x [doi]

Oh, J., & Levy, M. (2012). Neuromyelitis optica: An antibody-mediated disorder of the central nervous system. *Neurology Research International, 2012*, 460825. doi:10.1155/2012/460825 [doi]

Ontaneda, D., Hyland, M., & Cohen, J. A. (2012). Multiple sclerosis: New insights in pathogenesis and novel therapeutics. *Annual Review of Medicine, 63*, 389-404. doi:10.1146/annurev-med-042910-135833 [doi]

Ordonez Gallego, A., Gonzalez Baron, M., & Espinosa Arranz, E. (2007). Oxycodone: A pharmacological and clinical review. *Clinical & Translational Oncology : Official*

Publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico, 9(5), 298-307. doi:946 [pii]

Osborne, T. L., Raichle, K. A., Jensen, M. P., Ehde, D. M., & Kraft, G. (2006). The reliability and validity of pain interference measures in persons with multiple sclerosis. *Journal of Pain and Symptom Management, 32*(3), 217-229. doi:S0885-3924(06)00334-4 [pii]

Pachman, D. R., Weisbrod, B. L., Seisler, D. K., Barton, D. L., Fee-Schroeder, K. C., Smith, T. J., . . . Loprinzi, C. L. (2015). Pilot evaluation of scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer, 23*(4), 943-951. doi:10.1007/s00520-014-2424-8 [doi]

Paller, C. J., Campbell, C. M., Edwards, R. R., & Dobs, A. S. (2009). Sex-based differences in pain perception and treatment. *Pain Medicine (Malden, Mass.), 10*(2), 289-299. doi:10.1111/j.1526-4637.2008.00558.x [doi]

Pan, J., Zhao, P., Cai, H., Su, L., Wood, K., Shi, F. D., & Fu, Y. (2015). Hypoxemia, sleep disturbances, and depression correlated with fatigue in neuromyelitis optica spectrum disorder. *CNS Neuroscience & Therapeutics, 21*(7), 599-606. doi:10.1111/cns.12411 [doi]

Park, H. S., Sin, W. K., Kim, H. Y., Moon, J. Y., Park, S. Y., Kim, Y. C., & Lee, S. C. (2013). Scrambler therapy for patients with cancer pain - case series -. *The Korean Journal of Pain, 26*(1), 65-71. doi:10.3344/kjp.2013.26.1.65 [doi]

Pellkofer, H. L., Havla, J., Hauer, D., Schelling, G., Azad, S. C., Kuempfel, T., . . . Huge, V. (2013). The major brain endocannabinoid 2-AG controls neuropathic pain and mechanical hyperalgesia in patients with neuromyelitis optica. *PloS One, 8*(8), e71500. doi:10.1371/journal.pone.0071500 [doi]

Popescu, B. F., & Lucchinetti, C. F. (2016). Immunopathology: Autoimmune glial diseases and differentiation from multiple sclerosis. *Handbook of Clinical Neurology, 133*, 95-106. doi:10.1016/B978-0-444-63432-0.00006-2 [doi]

Qian, P., Lancia, S., Alvarez, E., Klawiter, E. C., Cross, A. H., & Naismith, R. T. (2012). Association of neuromyelitis optica with severe and intractable pain. *Archives of Neurology, 69*(11), 1482-1487. doi:1355367 [pii]

Rahim-Williams, B., Riley, J. L.,3rd, Williams, A. K., & Fillingim, R. B. (2012). A quantitative review of ethnic group differences in experimental pain response: Do biology, psychology, and culture matter? *Pain Medicine (Malden, Mass.), 13*(4), 522-540. doi:10.1111/j.1526-4637.2012.01336.x [doi]

Ricci, M., Pirotti, S., Scarpi, E., Burgio, M., Maltoni, M., Sansoni, E., & Amadori, D. (2012). Managing chronic pain: Results from an open-label study using MC5-A calmare(R) device. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer, 20*(2), 405-412. doi:10.1007/s00520-011-1128-6 [doi]

Ringelstein, M., Ayzenberg, I., Harmel, J., Lauenstein, A. S., Lensch, E., Stogbauer, F., . . . Kleiter, I. (2015). Long-term therapy with interleukin 6 receptor blockade in highly active

neuromyelitis optica spectrum disorder. *JAMA Neurology, 72*(7), 756-763. doi:10.1001/jamaneurol.2015.0533 [doi]

Rossi, S., Mataluni, G., Codeca, C., Fiore, S., Buttari, F., Musella, A., . . . Centonze, D. (2009). Effects of levetiracetam on chronic pain in multiple sclerosis: Results of a pilot, randomized, placebo-controlled study. *European Journal of Neurology, 16*(3), 360-366. doi:10.1111/j.1468-1331.2008.02496.x [doi]

Ruiz-Gaviria, R., Baracaldo, I., Castaneda, C., Ruiz-Patino, A., Acosta-Hernandez, A., & Rosselli, D. (2015). Specificity and sensitivity of aquaporin 4 antibody detection tests in patients with neuromyelitis optica: A meta-analysis. *Multiple Sclerosis and Related Disorders, 4*(4), 345-349. doi:10.1016/j.msard.2015.06.003 [doi]

Sabato, A. F., Marineo, G., & Gatti, A. (2005). Scrambler therapy. *Minerva Anestesiologica, 71*(7-8), 479-482.

Salinas, F. A., Lugo, L. H., & Garcia, H. I. (2012). Efficacy of early treatment with carbamazepine in prevention of neuropathic pain in patients with spinal cord injury. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists, 91*(12), 1020-1027. doi:10.1097/PHM.0b013e3182643c85 [doi]

Sapir, T., & Shoenfeld, Y. (2005). Facing the enigma of immunomodulatory effects of intravenous immunoglobulin. *Clinical Reviews in Allergy & Immunology, 29*(3), 185-199. doi:CRIAI:29:3:185 [pii]

Shi, Z., Chen, H., Lian, Z., Liu, J., Feng, H., & Zhou, H. (2016). Factors that impact health-related quality of life in neuromyelitis optica spectrum disorder: Anxiety, disability, fatigue and depression. *Journal of Neuroimmunology, 293*, 54-58. doi:10.1016/j.jneuroim.2016.02.011 [doi]

Silver, M., Blum, D., Grainger, J., Hammer, A. E., & Quessy, S. (2007). Double-blind, placebo-controlled trial of lamotrigine in combination with other medications for neuropathic pain. *Journal of Pain and Symptom Management, 34*(4), 446-454. doi:S0885-3924(07)00347-8 [pii]

Singh, A., Tetreault, L., Kalsi-Ryan, S., Nouri, A., & Fehlings, M. G. (2014). Global prevalence and incidence of traumatic spinal cord injury. *Clinical Epidemiology, 6*, 309-331. doi:10.2147/CLEP.S68889 [doi]

Sjolund, B. H. (2002). Pain and rehabilitation after spinal cord injury: The case of sensory spasticity? *Brain Research.Brain Research Reviews, 40*(1-3), 250-256. doi:S0165017302002072 [pii]

Sluka, K. A., Bjordal, J. M., Marchand, S., & Rakel, B. A. (2013). What makes transcutaneous electrical nerve stimulation work? making sense of the mixed results in the clinical literature. *Physical Therapy, 93*(10), 1397-1402. doi:10.2522/ptj.20120281 [doi]

Smith, T., Cheville, A. L., Loprinzi, C. L., & Longo-Schoberlein, D. (2017). Scrambler therapy for the treatment of chronic post-mastectomy pain (cPMP). *Cureus, 9*(6), e1378. doi:10.7759/cureus.1378 [doi]

Smith, T. J., Auwaerter, P., Knowlton, A., Saylor, D., & McArthur, J. (2017). Treatment of human immunodeficiency virus-related peripheral neuropathy with scrambler therapy: A case report. *International Journal of STD & AIDS, 28*(2), 202-204. doi:10.1177/0956462416656688 [doi]

Smith, T. J., Coyne, P. J., Parker, G. L., Dodson, P., & Ramakrishnan, V. (2010). Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A calmare(R)) for chemotherapy-induced peripheral neuropathy. *Journal of Pain and Symptom Management, 40*(6), 883-891. doi:10.1016/j.jpainsymman.2010.03.022 [doi]

Stadhouder, A., Buckens, C. F., Holtslag, H. R., & Oner, F. C. (2010). Are existing outcome instruments suitable for assessment of spinal trauma patients? *Journal of Neurosurgery.Spine, 13*(5), 638-647. doi:10.3171/2010.5.SPINE09128 [doi]

Stagg, N. J., Mata, H. P., Ibrahim, M. M., Henriksen, E. J., Porreca, F., Vanderah, T. W., & Philip Malan, T.,Jr. (2011). Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. *Anesthesiology, 114*(4), 940-948. doi:10.1097/ALN.0b013e318210f880 [doi]

Starkweather, A. R., Coyne, P., Lyon, D. E., Elswick, R. K.,Jr, An, K., & Sturgill, J. (2015). Decreased low back pain intensity and differential gene expression following calmare(R): Results from a double-blinded randomized sham-controlled study. *Research in Nursing & Health, 38*(1), 29-38. doi:10.1002/nur.21632 [doi]

Svendsen, K. B., Jensen, T. S., & Bach, F. W. (2004). Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? randomised double blind placebo controlled crossover

trial. *BMJ (Clinical Research Ed.), 329*(7460), 253. doi:10.1136/bmj.38149.566979.AE [doi]

Todd, A. J. (2010). Neuronal circuitry for pain processing in the dorsal horn. *Nature Reviews.Neuroscience, 11*(12), 823-836. doi:10.1038/nrn2947 [doi]

Transverse Myelitis Consortium Working Group. (2002). Proposed diagnostic criteria and nosology of acute transverse myelitis. *Neurology, 59*(4), 499-505.

Turcotte, D., Doupe, M., Torabi, M., Gomori, A., Ethans, K., Esfahani, F., . . . Namaka, M. (2015). Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: A randomized controlled trial. *Pain Medicine (Malden, Mass.), 16*(1), 149-159. doi:10.1111/pme.12569 [doi]

Tyler, E. J., Jensen, M. P., Engel, J. M., & Schwartz, L. (2002). The reliability and validity of pain interference measures in persons with cerebral palsy. *Archives of Physical Medicine and Rehabilitation, 83*(2), 236-239. doi:S0003-9993(02)12927-3 [pii]

Vollmer, T. L., Robinson, M. J., Risser, R. C., & Malcolm, S. K. (2014). A randomized, double-blind, placebo-controlled trial of duloxetine for the treatment of pain in patients with multiple sclerosis. *Pain Practice : The Official Journal of World Institute of Pain, 14*(8), 732-744. doi:10.1111/papr.12127 [doi]

Vranken, J. H., Dijkgraaf, M. G., Kruis, M. R., van der Vegt, M. H., Hollmann, M. W., & Heesen, M. (2008). Pregabalin in patients with central neuropathic pain: A randomized,

double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain, 136*(1-2), 150-157. doi:S0304-3959(07)00369-7 [pii]

Vranken, J. H., Hollmann, M. W., van der Vegt, M. H., Kruis, M. R., Heesen, M., Vos, K., . . . Dijkgraaf, M. G. (2011). Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: A randomized, double-blind, placebo-controlled trial. *Pain, 152*(2), 267-273. doi:10.1016/j.pain.2010.09.005 [doi]

Wardell, D. W., Rintala, D. H., Duan, Z., & Tan, G. (2006). A pilot study of healing touch and progressive relaxation for chronic neuropathic pain in persons with spinal cord injury. *Journal of Holistic Nursing : Official Journal of the American Holistic Nurses' Association, 24*(4), 231-40; discussion 241-4. doi:24/4/231 [pii]

Ware, J. E. (1994). SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute, New England Medical Center Hospitals.

Ware, J. E., Snow, K. K., Kosinski, M., & Gandek, B. (1994). SF-36 Health Survey: Manual and Interpretation Guide. Boston, MA: The Health Institute, New England Medical Center Hospitals.

Widerstrom-Noga, E. G., & Turk, D. C. (2003). Types and effectiveness of treatments used by people with chronic pain associated with spinal cord injuries: Influence of pain and psychosocial characteristics. *Spinal Cord, 41*(11), 600-609. doi:10.1038/sj.sc.3101511 [doi]

Wingerchuk, D. M. (2018). Immune-mediated myelopathies. *Continuum (Minneapolis, Minn.), 24*(2, Spinal Cord Disorders), 497-522. doi:10.1212/CON.0000000000000582 [doi]

Wingerchuk, D. M., Banwell, B., Bennett, J. L., Cabre, P., Carroll, W., Chitnis, T., . . . International Panel for NMO Diagnosis. (2015). International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology, 85*(2), 177-189. doi:10.1212/WNL.0000000000001729 [doi]

Wingerchuk, D. M., Hogancamp, W. F., O'Brien, P. C., & Weinshenker, B. G. (1999). The clinical course of neuromyelitis optica (devic's syndrome). *Neurology, 53*(5), 1107-1114.

Wingerchuk, D. M., Lennon, V. A., Lucchinetti, C. F., Pittock, S. J., & Weinshenker, B. G. (2007). The spectrum of neuromyelitis optica. *The Lancet.Neurology, 6*(9), 805-815. doi:S1474-4422(07)70216-8 [pii]

Wingerchuk, D. M., Lennon, V. A., Pittock, S. J., Lucchinetti, C. F., & Weinshenker, B. G. (2006). Revised diagnostic criteria for neuromyelitis optica. *Neurology, 66*(10), 1485-1489. doi:66/10/1485 [pii]

Wu, E. Q., Borton, J., Said, G., Le, T. K., Monz, B., Rosilio, M., & Avoinet, S. (2007). Estimated prevalence of peripheral neuropathy and associated pain in adults with diabetes in france. *Current Medical Research and Opinion, 23*(9), 2035-2042. doi:10.1185/030079907X210516 [doi]

Zhao, S., Mutch, K., Elsone, L., Nurmikko, T., & Jacob, A. (2014). Neuropathic pain in neuromyelitis optica affects activities of daily living and quality of life. *Multiple Sclerosis (Houndmills, Basingstoke, England), 20*(12), 1658-1661. doi:10.1177/1352458514522103 [doi]

Appendix A

Scrambler study inclusion & exclusion criteria

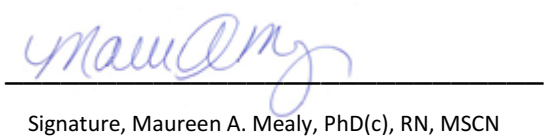
Inclusion Criteria	**Exclusion Criteria**
Diagnosis of NMOSD	Relapse within 6 months prior to enrollment
AQP-4 seropositivity	Diagnosis of peripheral neuropathy
≥18 years of age	Ongoing concomitant CNS disorder
Persistent pain (>3 months) rated at ≥4 on NRS pain scale	Patients who have used investigational agents or treatments for pain control within 30 days
CNP referable to lesion starting at or below C4	Pregnant or breastfeeding women
Stable medication regimen for ≥ 30 days prior to enrollment	Cognitive or mental incompetence
Able to read and understand English	Patients with implantable devices

Appendix B

Scrambler study patient event calendar

Phase	**Screening/Consent**	**Scrambler Therapy or Sham Treatment (Treatment Phase)**										**Follow-up (days)**	
Time Point (days)	Within 2 weeks	1	2	3	4	5	6	7	8	9	10	30 days following end of treatment	60 days following end of treatment
Exam/Tests*	Neurologic Exam, MRI review, Q[#]	AE and daily NRS pain score assessment during treatment phase (days 1-10)									Q[#]	NRS pain score, Q[#]	NRS pain score, Q[#]
[#]Q: Questionnaires (BPI; Neuro-QoL SF, – anxiety, – depression,– sleep disturbance)													

Curriculum Vitae for Academic Promotion
The Johns Hopkins University School of Medicine



Signature, Maureen A. Mealy, PhD(c), RN, MSCN Date: 3/3/2019

DEMOGRAPHIC AND PERSONAL INFORMATION

Current Appointments

2015 – present	PhD Candidate **Johns Hopkins University**
2010 – present	Clinical Research Program Manager Neuromyelitis Optica Clinic **Johns Hopkins University School of Medicine**
2010 – present	Senior Research Nurse, Multiple Sclerosis and Transverse Myelitis Centers Division of Neuroimmunology Department of Neurology **Johns Hopkins University School of Medicine**

Personal Data

Maureen A. Mealy, PhD(c), RN, MSCN
600 North Wolfe Street
Pathology 627
Baltimore, MD 21287
Phone: 410-502-8672
FAX: 410-502-6736
email: mmealy1@jhmi.edu

Education and Training

1992 – 1996	Bachelor of Science, Psychology **University of Maryland** (College Park, MD)
1997 – 1999	Bachelor of Science, Nursing **Johns Hopkins University** (Baltimore, MD)
2015 – present	Doctor of Philosophy, Nursing **Johns Hopkins University** (Baltimore, MD)

Professional Experience

2010 – present	Neuromyelitis Optica Clinical Research Program Manager *Department of Neurology* **Johns Hopkins University School of Medicine** (Baltimore, MD)

2010 – 2015	Clinical Program Manager Transverse Myelitis Center, *Department of Neurology* **Johns Hopkins University School of Medicine** (Baltimore, MD)
2010 – 2011	Neuromyelitis Optica Consortium Administrative Director *Department of Neurology* **Johns Hopkins University School of Medicine** (Baltimore, MD)
2009 – 2010	Clinical Research Manager, Transverse Myelitis & Neuromyelitis Optica Clinic *Department of Neurology* **University of Texas Southwestern** (Dallas, TX)
2009 – 2010	Clinical Research Manager, Pediatric Demyelinating Disease Center *Department of Neurology* **Children's Health** (Dallas, TX)
2007 – 2008	Senior Research Nurse, Multiple Sclerosis, Transverse Myelitis, and Encephalitis Centers *Department of Neurology* **Johns Hopkins University School of Medicine** (Baltimore, MD)
2005 – 2007	Neurosciences Clinical Nurse Coordinator *Departments of Neurology and Neurosurgery* **Johns Hopkins Hospital** (Baltimore, MD)
2000 – 2007	Nurse Clinician III Neurosciences Critical and Progressive Care Units, *Departments of Neurology and Neurosurgery* **Johns Hopkins Hospital** (Baltimore, MD)

RESEARCH ACTIVITIES

Peer-Reviewed Publications

Original Science Research

1. **Mealy MA,** Newsome SD, Greenberg BM, Wingerchuk D, Calabresi PA, Levy M. Lower serum vitamin D levels are associated with recurrent inflammatory spinal cord disease. *Arch Neurol*. 2011 Nov 14.
2. **Mealy MA,** Greenberg BM, Wingerchuk DM, Levy M. Epidemiology of neuromyelitis optica in the United States: a multicenter analysis. *Arch Neurol.* 2012 Jun 25:1-5.
3. Sotirchos ES, Saidha S, Byraiah G, **Mealy MA,** Ibrahim MA, Sepah YJ, Newsome SD, Ratchford JN, Frohman EM, Balcer LJ, Crainiceanu CM, Nguyen QD, Levy M, Calabresi PA. In-vivo identification of morphologic retinal abnormalities in neuromyelitis optica. *Neurology*. 2013 Apr 9;80(15):1406-14.
4. Kremer L, **Mealy M,** Jacob A, Nakashima I, Cabre P, Bigi S, Paul F, Jarius S, Aktas O, Elsone L, Mutch K, Levy M, Takai Y, Collongues N, Banwell B, Fujihara K, de Seze J. Brainstem

manifestations in neuromyelitis optica: a multicenter study of 258 patients. *Mult Scler.* 2013 Oct 7.

5. **Mealy MA,** Wingerchuk DM, Palace J, Greenberg BM, Levy M. Comparison of Relapse and Treatment Failure Rates Among Patients With Neuromyelitis Optica: Multicenter Study of Treatment Efficacy. *JAMA Neurol*. 2014 Mar;71(3):324-30.
6. Kimbrough DJ, **Mealy MA,** Simpson A, Levy M. Predictors of Recurrence Following an Initial Episode of Transverse Myelitis. *Neurol Neuroimmunol Neuroinflamm*. 2014 Apr 24;1(1):e4.
7. **Mealy MA** and Levy M. Purified human C1-esterase inhibitor is safe in acute relapses of neuromyelitis optica. *Neurol Neuroimmunol Neuroinflamm*. 2014 Apr 24;1(1):e5.
8. **Mealy MA,** Whetsone A, Orman G, Izbudak I, Calabresi PA, Levy M. Longitudinally extensive optic neuritis as an MRI biomarker distinguishes neuromyelitis optica from multiple sclerosis. *J Neurol Sci.* 2015 Aug 15;355(1-2):59-63.
9. Pekcevik Y, Mitchell CH, **Mealy MA,** Orman G, Lee IH, Newsome SD, Thompson CB, Pardo CA, Calabresi PA, Levy M, Izbudak I. Differentiating neuromyelitis optica from other causes of longitudinally extensive transverse myelitis on spinal magnetic resonance imaging. *Mult Scler*. 2015 Jul 24.
10. **Mealy MA,** Kyong S, John G and Levy M. Bevacizumab is safe in acute relapses of neuromyelitis optica. *Clin Exp Neuroimmunol.* 24 Aug 2015 DOI: 10.1111/cen3.12239
11. **Mealy MA** and Levy M. Favorable outcome of granulocyte colony-stimulating factor use in neuromyelitis optica patients presenting with agranulocytosis in the setting of rituximab. *J Neuroimmunol.* 2015 Oct 15;287:29-30.
12. Hollinger KR, Franke C, Arenivas A, Woods SR, **Mealy MA,** Levy M, Kaplin AI. Cognition, Mood, and purpose in life in neuromyelitis optica spectrum disorder. *JNS.* 2016 January 11;362:85-90.
13. Abboud H, Petrak A, **Mealy M,** Sasidharan S, Siddique L, Levy M. Treatment of acute relapses in neuromyelitis optica: Steroids alone versus steroids plus plasma exchange. *Mult Scler.* 2016 Feb;22(2):185-92. doi: 10.1177/1352458515581438. Epub 2015 Apr 28.
14. Abboud H, Fernandez HH, **Mealy MA**, Michael Levy M. Spinal Movement Disorders in Neuromyelitis Optica: An Under-recognized Phenomenon. *MDCP.* In press, accepted 8 December 2015. DOI:10.1002/mdc3.12321
15. Kessler RA, **Mealy MA**, Levy M. Early indicators of relapses vs pseudorelapses in neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm.* 2016 Jul 28;3(5):e269. doi: 10.1212/NXI.0000000000000269. eCollection 2016 Oct.
16. **Mealy MA,*** Chavarro VS,* Simpson A, Lacheta A, Pache F, Ruprecht K, Gold SM, Paul F, Brandt AU, Levy M. Insufficient treatment of severe depression in neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm*. 2016 Oct 24;3(6):e286. eCollection 2016. PMCID: PMC5079380
17. Barreras P, **Mealy MA,** Pardo CA. TNF-alpha inhibitor associated myelopathies: A neurological complication in patients with rheumatologic disorders. *J Neurol Sci.* 2017 Feb 16;373:303-6. Available online at http://dx.doi.org/10.1016/j.jns.2017.01.023
18. Orman G, Wang KY, Pekcevik Y, Thompson CB, **Mealy M**, **Levy** M, Izbudak I. Enhancing Brain Lesions during Acute Optic Neuritis and/or Longitudinally Extensive Transverse Myelitis May

Portend a Higher Relapse Rate in Neuromyelitis Optica Spectrum Disorders. *Am J Neuroradiol.* 2017 May;38(5):949-953. doi: 10.3174/ajnr.A5141. Epub 2017 Mar 16. PMID: 28302609

19. Bove R, Elsone L, Alvarez E, Borisow N, Cortez MM, Mateen FJ, **Mealy MA**, Mutch K, Tobyne S, Ruprecht K, Buckle G, Levy M, Wingerchuk DM, Paul F, Cross AH, Weinshenker B, Jacob A, Klawiter EC, Chitnis T. Female hormonal exposures and neuromyelitis optica symptom onset in a multicenter study. *Neurol Neuroimmunol Neuroinflamm*. 2017 Mar 24;4(3):e339. doi: 10.1212/NXI.0000000000000339. eCollection 2017 May.
20. Vadivelu S, Vadivelu S, **Mealy M**, Patel S, Kosnik-Infinger L, Becker D. Chiari I malformation in children with transverse myelitis. *Dev Neurorehabil.* 2017 May 24:1-6. doi: 10.1080/17518423.2017.1323972. [Epub ahead of print]
21. Eaneff S, Wanga V, Hangera M, Levy M, **Mealy MA**, Brandt AU, Eek D, Ratchford JN, Nyberg F, Goodall J, Wicks P. Patient Perspectives on Neuromyelitis Optica Spectrum Disorders: Data from the PatientsLikeMe Online Community. *Mult Scler Relat Disord.* Received 2 February 2017, Revised 8 July 2017, Accepted 11 July 2017, Available online 11 July 2017.
22. **Mealy MA**, Kim SH, Schmidt F, López R, Jimenez Arango JA, Paul F, Wingerchuk DM, Greenberg BM, Kim HJ, Levy M. Aquaporin-4 serostatus does not predict response to immunotherapy in neuromyelitis optica spectrum disorders. *Mult Scler.* 2017 Aug 1:1352458517730131. doi: 10.1177/1352458517730131. [Epub ahead of print]
23. Kessler RA, **Mealy MA,** Jimenez-Arango JA, Quan C, Paul F, López R, Hopkins S, Levy M. Anti-aquaporin-4 titer is not predictive of disease course in neuromyelitis optica spectrum disorder: A multicenter cohort study. *Mult Scler Relat Disord.* 2017 Oct;17:198-201. doi: 10.1016/j.msard.2017.08.005. Epub 2017 Aug 16.
24. Abboud H, Rossman I, **Mealy MA,** Hill E, Thompson N, Banerjee A, Probasco J, Levy M. Neuronal autoantibodies: differentiating clinically relevant and clinically irrelevant results. *J Neurol.* 2017 Nov;264(11):2284-2292. doi: 10.1007/s00415-017-8627-4. Epub 2017 Oct 3.
25. Klawiter EC, Bove R, Elsone L, Alvarez E, Borisow N, Cortez M, Mateen F, **Mealy MA,** Sorum J, Mutch K, Tobyne SM, Ruprecht K, Buckle G, Levy M, Wingerchuk D, Paul F, Cross AH, Jacobs A, Chitnis T, Weinshenker B. High risk of postpartum relapses in neuromyelitis optica spectrum disorder. *Neurology.* 2017 Nov 28;89(22):2238-2244. doi: 10.1212/WNL.0000000000004681. Epub 2017 Nov 1.
26. Barreras P, Fitzgerald KC, **Mealy MA,** Jimenez JA, Becker D, Newsome SD, Levy M, Gailloud P, Pardo CA. Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy. *Neurology.* 2017 Dec 1. pii: 10.1212/WNL.0000000000004765. doi: 10.1212/WNL.0000000000004765. [Epub ahead of print]
27. Schwartz K, Wymbs NF, Huang H, **Mealy MA,** Pardo CA, Zackowski K, Levy M. Randomized, Placebo-controlled Crossover Study of Dalfampridine Extended-release in Transverse Myelitis. *Mult Scler J Exp Transl Clin.* 2018 Jan 2;90(1):e12-e21. doi: 10.1212/WNL.0000000000004765. Epub 2017 Dec 1.
28. Kessler RA, Li X, Schwartz K, **Mealy MA,** Levy M. Two-year observational study of deferiprone in superficial siderosis. *CNS Neurosci Ther.* 2018 Mar;24(3):187-192. doi: 10.1111/cns.12792. Epub 2017 Dec 28.

29. **Mealy MA,** Nam T, Pardo SJ, Pardo CA, Sobreira NL, Avramopoulos D, Valle D, Burns KH, Levy M. Familial monophasic acute transverse myelitis due to pathogenic variant in *VPS37A. Neurol Genet.* 2018 Jan 30;4(1):e213. doi: 10.1212/NXG.0000000000000213. eCollection 2018 Feb.
30. **Mealy MA**, Cook LJ, Pache F, Velez DL, Borisow N, Becker D, Jimenez Arango JA, Paul F, Levy M. Vaccines and the association with relapses in patients with neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord*. 2018 Jul;23:78-82. doi: 10.1016/j.msard.2018.05.003. Epub 2018 May 7.
31. D'Amato SJ, **Mealy MA,** Erdek MA, Kozachik S, Smith TJ. Scrambler Therapy for the Treatment of Chronic Central Pain: A Case Report. *A A Pract*. 2018 Jun 15;10(12):313-315. doi: 10.1213/XAA.0000000000000695.
32. **Mealy MA**, Kessler RA, Rimler Z, Reid A, Totonis L, Cutter G, Kister I, Levy M. Mortality in neuromyelitis optica is strongly associated with African ancestry. *Neurol Neuroimmunol Neuroinflamm.* 2018 Jun 7;5(4):e468. doi: 10.1212/NXI.0000000000000468. eCollection 2018Jul.
33. **Mealy MA,** Boscoe A, Caro J, Levy M. Assessment of Patients with Neuromyelitis Optica Spectrum Disorder Using EQ-5D. *Int J MS Care*. In-Press. Online ahead of print: doi.org/10.7224/1537-2073.2017-076.
34. **Mealy MA,** Newsome SD, Kozachik SL, Levy M. Smith TJ. Scrambler Therapy for Treatment-Resistant Central Neuropathic Pain in a Patient with Transverse Myelitis: A Case Report. *Int J MS Care*. In-Press. Online ahead of print: https://doi.org/10.7224/1537-2073.2017-083.
35. Kim SH, **Mealy MA**, Levy M, Schmidt F, Ruprecht K… Kim HJ. Racial differences in neuromyelitis optica spectrum disorder. *Neurology*. 2018 Nov 27;91(22):e2089-e2099. doi: 10.1212/WNL.0000000000006574. Epub 2018 Oct 26.
36. McCreary M, **Mealy MA**, Wingerchuk DM, Levy M, DeSena A, Greenberg BM. Updated diagnostic criteria for neuromyelitis optica spectrum disorder: Similar outcomes of previously separate cohorts. *Mult Scler J Exp Transl Clin.* 2018 Dec 6;4(4):2055217318815925. doi: 10.1177/2055217318815925. eCollection 2018 Oct-Dec.
37. **Mealy MA,** Mossburg SE, Kim SH, Messina S, Borisow N… Levy M. Long-term disability in neuromyelitis optica spectrum disorder with a history of myelitis is associated with age at onset, delay in diagnosis/preventive treatment, MRI lesion length and presence of symptomatic brain lesions. *Mult Scler Relat Disord.* 2018 Dec 9;28:64-68. doi: 10.1016/j.msard.2018.12.011. [Epub ahead of print]
38. Banerjee A, Ng J, Coleman J, Ospina JP, **Mealy M,** Levy M. Outcomes from acute attacks of neuromyelitis optica spectrum disorder correlate with severity of attack, age and delay to treatment. *Mult Scler Relat Disord.* 2018 Dec 10;28:60-63. doi: 10.1016/j.msard.2018.12.010. [Epub ahead of print]

Editorials

1. Greenberg BM, Wingerchuk D, **Mealy M,** Levy M. What is the true clinicopathologic spectrum of neuromyelitis optica?-Reply. *JAMA Neurol.* 2013 Feb;70(2):272-3.
2. Levy M, **Mealy MA,** Kimbrough DJ, Simpson A. Impact of Vitamin D in Recurrent Transverse Myelitis. *Neurol Neuroimmunol Neuroinflamm*. Published online April 24, 2014 1:e4

Reviews

1. Pekcevik Y, Orman G, Lee IH, **Mealy MA,** Levy M, Izbudak I. What do we know about brain contrast enhancement patterns in neuromyelitis optica? *Clin Imaging.* 2015 Jul 26. pii: S0899-7071(15)00206-5. doi: 10.1016/j.clinimag.2015.07.027. [Epub ahead of print] Review.
2. Kessler RA, **Mealy MA,** Levy M. Treatment of Neuromyelitis Optica Spectrum Disorder: Acute, Preventive, and Symptomatic. *Curr Treat Options Neurol.* 2016 Jan;18(1):2. doi: 10.1007/s11940-015-0387-9.
3. MOG antibody disease: A review of MOG antibody seropositive neuromyelitis optica spectrum disorder. Narayan R, Simpson A, Fritsche K, Salama S, Pardo S, **Mealy M**, Paul F, Levy M. *Mult Scler Relat Disord.* 2018 Jul 23;25:66-72. doi: 10.1016/j.msard.2018.07.025. [Epub ahead of print] Review.

Abstracts and Professional Presentations

1. Harder L., Arenivas A, **Mealy M,** & Greenberg B. (2010, June). Neuropsychological functioning in pediatric demyelinating disease populations: A preliminary comparison of performance between multiple sclerosis (MS) and transverse myelitis (TM) patient groups. *The Clinical Neuropsychologist,* 24(4). Poster presented at the annual convention of the American Academy of Clinical Neuropsychology (AACN). *Chicago, Illinois.*
2. Harder L., Arenivas A, **Mealy M,** & Greenberg B. (2010, June). The role of neuropsychology in a multi-disciplinary clinic to treat pediatric demyelinating diseases. *The Clinical Neuropsychologist,* 24(4). Poster presented at the annual convention of the American Academy of Clinical Neuropsychology (AACN). *Chicago, Illinois.*
3. Arenivas A., Harder L., **Mealy M,** & Greenberg B. (2010, June). Psychosocial Functioning, Academic Performance, and Utilization of School Services in Pediatric Demyelinating Diseases: Preliminary Findings. *The Clinical Neuropsychologist,* 24(4). Poster presented at the annual convention of the American Academy of Clinical Neuropsychology (AACN). *Chicago, Illinois.*
4. **Mealy MA,** Newsome S, Calabresi PA, & Levy M. (2011, April). A Comparison of Vitamin D Levels in Patients with Idiopathic TM and NMO/Recurrent TM. Poster presentation at an Integrated Neuroscience Session at the annual conference of the American Academy of Neurology (AAN). *Honolulu, Hawaii.*
5. Taylor SL, Noll K, Courtney A, Graves D, Frohman E, **Mealy M,** Lacritz L, & Greenberg B. (2011, April). Lack of the PASAT, SDMT, or Judgment of Line Tests to Detect Cognitive Impairment in a Cohort with Demyelinating Disease. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Honolulu, Hawaii.*
6. **Mealy MA,** Jimenez JA, Gailloud P, Becker D, Newsome SD, Levy M, Pardo-Villamizar, CA. (2013, March). Differentiating Vascular Myelopathy from Transverse Myelitis. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *San Diego, CA.*
7. Vadivelu S, Vadivelu S, **Mealy MA,** Becker D. (2013, Sept). Increased incidence of Chiari 1 malformations in children with transverse myelitis. Poster presentation at the American Academy of Physical Medicine & Rehabilitation (AAPM&R) Annual Assembly. *National Harbor, MD.*

8. **Mealy MA,** Whetstone A, Calabresi PA, Levy M. (2014, April) Differentiating NMO and MS-associated optic neuritis by MRI. Platform Presentation at the annual conference of the American Academy of Neurology (AAN). *Philadelphia, PA.*
9. **Mealy MA,** Becker D, Newsome SD, Ratchford JN, Levy M, Pardo CA. (2014, April). Differential Diagnosis of Transverse Myelitis. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Philadelphia, PA.*
10. Jimenez Arango JA, **Mealy MA,** Becker D, Gailloud P, Pardo-Villamizar CA. (2014, April). A Note of Caution about the Diagnosis and Treatment of Suspected Transverse Myelitis. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Philadelphia, PA.*
11. Levy M, **Mealy MA,** (2014, April). Trial of C1-Esterase Inhibitor in Acute Relapses of Neuromyelitis Optica. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Philadelphia, PA.*
12. Abboud H, Petrak A, **Mealy MA,** Sasidharan S, Siddique L, Levy M. (2014, September). Retrospective Review of Optimal Treatment for Acute Relapses in Neuromyelitis Optica. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *Boston, MA.*
13. Barreras PV, **Mealy MA,** Jimenez JA, Reyes-Mantilla MI, Becker D, Ratchford JN, Newsome SN, Levy M, Gailloud P, Pardo CA. (2014, October). Temporal Profiles and Clinical Biomarkers in the Differential Diagnosis of Transverse Myelitis. Poster presentation at the annual meeting of the American Neurological Association (ANA). *Baltimore, MD.*
14. Abboud H, **Mealy MA,** Levy M. (2015, April). Spinal movement disorders in NMO Patients: An Under-recognized Phenomenon. Platform presentation at the annual conference of the American Academy of Neurology (AAN). *Washington, DC.*
15. Kremer L, Asgari N, **Mealy M,** Mutch K, Levy M, Jacob A, Collongues N, De Seze J. (2015, April). Tobacco Smoking and Severity of Neuromyelitis Optica. Platform presentation at the annual conference of the American Academy of Neurology (AAN). *Washington, DC.*
16. **Mealy MA,** Paul F, Aktas O, Broadley S, Cabre P, Han M, Jacob A, John G, Kim HJ, Kimbrough D, Klawiter E, Kleiter I, Leite MI, Marignier R, Matiello M, Nakashima I, Palace J, Repovic P, Ringelstein M, Sato D, Schippling S, Traboulsee A, Waters P, Weinshenker B, Wingerchuk D, & Levy M on behalf of the Guthy Jackson Charitable Foundation-ICC&BR. (2015, April). New Acute Severity Scale for Neuromyelitis Optica Relapses. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Washington, DC.*
17. **Mealy MA,** Shin K, John G, Levy M. (2015, April). Bevacizumab is Safe in Acute Relapses of Neuromyelitis Optica. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Washington, DC.*
18. Dukandar J, Chen J, **Mealy MA,** Gailloud P, Pardo CA, Levy M. (2015, April). Distinguishing spinal dural arteriovenous fistulas from idiopathic transverse myelitis: a retrospective study of 94 patients. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Washington, DC.*
19. Barreras P, **Mealy M,** Pardo-Villamizar C. (2015, April). TNF-alpha Inhibitor Associated Myelopathies: A Neurological Complication in Patients with Rheumatologic Disorders. Poster

presentation at the annual conference of the American Academy of Neurology (AAN). *Washington, DC.*

20. Arenivas A, **Mealy MA,** Rahn K, Franke C, Kaplin A, Levy M. (2015, October). Processing Speed and Informant Reports of Executive Functioning in Neuromyelitis Optica. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Washington, DC.*
21. **Mealy MA,** Cook LJ, Pache F, Borisow N. Velez DI, Becker D, Jimenez Arango JA, Paul F, Levy M. (2015, October). Do Vaccinations Trigger Relapses in Neuromyelitis Optica? Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *Barcelona, Esp.*
22. Pekcevik Y, Mitchell CH, **Mealy MA,** Orman G, Lee IH, Newsome SD, Thompson CB, Pardo CA, Calabresi PA, Levy M, Izbudak I. (2015, October). Differentiating neuromyelitis optica from other causes of longitudinally extensive transverse myelitis on spinal magnetic resonance imaging. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *Barcelona, Esp.*
23. Orman G, Pekcevik Y, Thompson C, **Mealy M,** Levy M, Izbudak I. (2015, October). Brain contrast enhancement in neuromyelitis optica: its relation to acute attacks and clinical disease severity. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *Barcelona, Esp.*
24. Orman G, Pekcevik Y, Thompson C, Siddique L, **Mealy M,** Levy M, Izbudak I. (2015, October). Longitudinal evolution of neuromyelitis optica brain lesions on MRI and correlation to disability scores. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *Barcelona, Esp.*
25. **Mealy MA,** Button J, Al-Louzi O, Orman G, Jazebi N, Izbudak I, Calabresi PA, Saidha S, Levy M. (2016, April). MRI Lesion Length in Acute Optic Neuritis Correlates with Degree of Inner Retinal Thinning in Multiple Sclerosis. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Vancouver, CA.*
26. Bove R, Elsone L, Alvarez E, Borisow N, Cortez M, Mateen F, **Mealy M,** Sorum J, Mutch K, Tobyne S, Ruprecht K, Buckle G, Levy M, Wingerchuk D, Friedemann P, Cross A, Weinshenker B, Jacob A, Klawiter E, Chitnis T. (2016, April). Hormonal Exposures Relate to Clinical Phenotype in Women with Neuromyelitis Optica. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Vancouver, CA.*
27. Schwartz K, **Mealy MA**, Levy, M. (2016, April). Treatment of Acute Relapses in Transverse Myelitis: Steroids Alone Versus Steroids Plus Plasma Exchange. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Vancouver, CA.*
28. **Mealy MA,** Yeshokumar A, Mossburg SE, Levy M. (2016, April). Long Term Disability in Neuromyelitis Optica Spectrum Disorder Is Associated with Number of Relapses, MRI Lesion Length and Race. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Vancouver, CA.*
29. Abboud H, Rossman I, **Mealy M,** Levy M. (2016, April). Rates of True Positives and False Positives in Paraneoplastic Antibody Testing in Neurological Diseases. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Vancouver, CA.*

30. **Mealy MA,*** Chavarro VS,* Pache F, Lacheta A, Ruprecht K, Simpson A, Paul F, Brandt A, Levy M. (2016, April). Pain, Fatigue and Depression in Patients with Neuromyelitis Optica Spectrum Disorder in Europe and USA. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Vancouver, CA.*
31. Kessler R, **Mealy MA,** Levy M. (2016, April). Early Predictors of Relapses versus Pseudorelapses in Neuromyelitis Optica Spectrum Disorder. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Vancouver, CA.*
32. **Mealy MA,** Simpson A, Levy M. (2016, September). Comparing the Burden of Symptom Severity among Autoimmune Diseases affecting the Spinal Cord. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *London, UK.*
33. Zackowski KM, Schwartz K, Wymbs N, Huang H, Jiang A, Becker D, Celnik PA, Pardo CA, **Mealy MA,** Levy M. (2016, September). Phase II, placebo-controlled, double-blinded, crossover study of dalfampridine-extended release (D-ER) in monophasic transverse myelitis. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *London, UK.*
34. Levy M & **Mealy MA.** (2016, September). Phase I, Open Label Safety Study of Ublituximab for the Treatment of Acute Neuromyelitis Optica Relapses. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *London, UK.*
35. Kessler RA, **Mealy MA**, Jimenez-Arango JA, Quan C, Paul F, López R, Hopkins S, Levy M. (2016, September). Anti-Aquaporin-4 Titer Is Not Predictive of Disease Course in Neuromyelitis Optica. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *London, UK.*
36. Cook LJ, Rose JW, Alvey J, Jolley AM, Kuhn R, Marron B, Pederson M, Enriquez R, Yearley J, Dean JM , Han MH, Feng M, Ganaway T, Levy M, **Mealy M**… Behne J. (2016, September). A comparison of seropositive and seronegative patients in the Collaborative International Research in Clinical and Longitudinal Experience for NMOSD Studies (CIRCLES) registry. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *London, UK.*
37. Cook LJ, Rose JW, Jolley AM, Alvey J, Kuhn R, Pederson M, Han M, Levy M, **Mealy M**… Behne J. (2016, September). The CIRCLES program: accelerating solutions to neuromyelitis optica spectrum disorder. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *London, UK.*
38. **Mealy MA**, Kim S, Schmidt F, Lopez R, Jimenez Arango JA, Paul F, Wingerchuk DM, Greenberg BM, Kim HJ, Levy M. (2017, April). Aquaporin-4 serostatus does not predict response to immunotherapy in neuromyelitis optica spectrum disorders. Platform presentation at the annual conference of the American Academy of Neurology (AAN). *Boston, MA.*
39. Ng JC, Coleman J, Ospina J, Levy M, **Mealy MA.** (2017, April). Treatment of acute NMO relapses: Earlier does not necessarily mean better. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Boston, MA.*

40. Kessler RA, **Mealy MA,** Levy M. (2017, April). Clinical predictors of death in neuromyelitis optica spectrum disorder. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Boston, MA.*
41. Gordon-Lipkin E, **Mealy MA,** Ferenc L, Ryan M, Levy M, Arenivas A. (2017, April). Neuropsychological Profiles in Pediatric Neuromyelitis Optica Spectrum Disorder. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Boston, MA.*
42. Kessler RA, Schwartz, Li X, **Mealy MA,** Levy M. (2017, April). Two-Year Observational Study of Deferiprone in Superficial Siderosis. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Boston, MA.*
43. Pardo S, **Mealy MA**, Nam T, Burns KH, Levy M. Familial Transverse Myelitis Associated with Mutation in VPS37A Gene. (2017, April). Platform presentation at the annual conference of the American Academy of Neurology (AAN). *Boston, MA.*
44. **Mealy MA,** Cook LJ, Pache F, Borisow N, Velez-Sierra DL, Becker D, Jimenez Arango JA, Paul F, Levy M. (2017, October). Vaccines and the risk of relapse in patients with neuromyelitis optica spectrum disorder. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *Paris, FR.*
45. Banerjee A, Coleman J, Ng JC, Ospina J, **Mealy MA**, Levy M. (2017, October). Point of no return: outcomes from acute relapses of neuromyelitis optica depend on severity. Poster presentation at the annual conference of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). *Paris, FR.*
46. **Mealy MA,** Cabahug P, Levy M. The Effect of Sexual Dysfunction on Quality of Life in Women with Neuromyelitis Optica Spectrum Disorder. (2018, April). Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Los Angeles, CA.*
47. **Mealy MA,** Munoz Arcos L, Barreras P, Garcia M, Becker D, Newsome SD, Gailloud PH, Levy M, Pardo CA. It's Not All Transverse Myelitis: The Differential Diagnosis of Spinal Cord Myelopathy. (2018, April). Platform presentation at the annual conference of the American Academy of Neurology (AAN). *Los Angeles, CA.*
48. **Mealy MA**, Mossburg SE, Kim SH, Messina S, Borisow N, Lopez R, Ospina JP, Scheel M, Yeshokumar A, Amine A, Jimenez JA, Paul F, Palace J, Kim HJ, Levy M. Contributors to long-term disability in patients with neuromyelitis optica spectrum disorder. (2018, April). Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Los Angeles, CA.*
49. Munoz Arcos L, Gordon-Lipkin E, Barreras P, Castaneda MJ, **Mealy MA,** Piedra W, Murphy O, Levy M, Becker D, Newsome SD, Pardo CA. The spectrum of myelopathies in children: Beyond idiopathic transverse myelitis. Poster presentation at the annual conference of the American Academy of Neurology (AAN). *Los Angeles, CA.*
50. **Mealy MA,** Kozachik SL, Newsome SD, Nolan MT, Smith TJ, Levy M. Scrambler Therapy: Potential New Treatment for Central Neuropathic Pain? (2018, June). Poster presentation at the annual conference of the Consortium of Multiple Sclerosis Centers. (CMSC). Nashville, TN.

Extramural Sponsorship

9/1/2017-6/1/2018	TL1 TR001078 from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research.

Research Coordination

2007 – 2014	Novartis CFTY720D2309, multi-center Phase III study of fingolimod for daily management of multiple sclerosis
2007 – 2014	Accelerated Cure Project, multi-center longitudinal epidemiologic study looking into the causes of demyelinating diseases
2009 – 2010	Multiple Sclerosis Cognition Study, single-center longitudinal study of cognitive dysfunction in multiple sclerosis patients
2010 – 2011	Multiple Sclerosis Vitamin D Study, single-center pilot study examining the safety and effects on immune profile of cholecalciferol on patients with multiple sclerosis
2010 – 2011	Guthy-Jackson Charitable Foundation NMO Consortium, multi-center cohort study aimed at characterizing epidemiologic factors in NMO
2012 – 2015	Dalfampridine in transverse myelitis study in collaboration with Acorda Therapeutics, single-center study to test the efficacy of sustained release oral dalfampridine in TM
2013 – 2014	CINRYZE® (C1 esterase inhibitor [human]) for the treatment of acute optic neuritis and/or transverse myelitis in neuromyelitis optica and neuromyelitis optica spectrum disorder, single-center open-label pilot study to examine the safety and efficacy of Cinryze for acute management of neuromyelitis optica
2013 – 2015	Bevacizumab (Avastin) for the treatment of acute NMO exacerbations in collaboration with Genentech and Guthy-Jackson Charitable Foundation, single center open-label pilot study to examine the safety and efficacy of bevacizumab for the treatment of acute optic neuritis and/or transverse myelitis in neuromyelitis optica and neuromyelitis optica spectrum disorder
2015 – 2017	Ublituximab for the treatment of acute neuromyelitis optica spectrum disorder exacerbations in collaboration with TG Therapeutics, single-center open-label pilot study to examine the safety and efficacy of ublituximab for acute management of neuromyelitis optica exacerbations
2017 – present	Phase II Randomized, Single Blind Sham-Controlled Research Study Investigating Scrambler Therapy for Neuropathic Pain caused by Neuromyelitis Optica Spectrum Disorder

EDUCATIONAL ACTIVITIES

Teaching

May 2007	Reviewer, *CME/CNE course: Mastering Multiple Sclerosis: Practical Strategies for Challenging Cases* (Washington, DC)

2007 – 2008	Instructor, *Clinical Topics in Neuroscience Nursing: Multiple Sclerosis Workshop*, Department of Neurology and Neurosurgery, Johns Hopkins Hospital (Baltimore, MD)
2009 – 2010	Instructor, *National Multiple Sclerosis Society Nurse and Physician Extender Training Program: Pediatric Multiple Sclerosis*, Department of Neurology, University of Texas Southwestern Medical Center (Dallas, TX)
2011 – 2012	Instructor, *NeuroAcademy: Patient Care Management, Transverse Myelitis Workshop,* Department of Neurology and Neurosurgery, Johns Hopkins Hospital (Baltimore, MD)

Mentoring

2009 – 2010	Ana Arenivas, pre-doctoral fellow at University of Texas Southwestern, mentored in Pediatric Demyelinating Disease Clinic. Dr. Arenivas is currently a PhD neuropsychologist at TIRR Memorial Hermann Institute for Rehabilitation and Research in Houston.
2015 – 2016	Anusha Yeshokumar, Neurology resident at Johns Hopkins University, mentored on a project involving disability in NMO. Dr. Yeshokumar is currently a faculty pediatric neurologist at Mount Sinai Health System in New York.
2015 – 2017	Jennifer Ng, Master's in Nursing at Johns Hopkins University, mentoring for Research Honors Program with NMOSD project, for which results were presented at the American Academy of Neurology. Ms. Ng is currently employed in the Neonatal ICU in Children's Memorial Hermann Hospital.
2016 – 2017	Juan Pablo Ospina, Medical Student at Universidad el Bosque, mentored during clinical rotation at Johns Hopkins University Department of Neurology on a project involving disability and treatment in NMO.
2016 – present	Kate Schwartz, Licensed Practical Nurse at Johns Hopkins University, act as her direct supervisor for clinical trials including Dalfampridine in Transverse Myelitis and Eculizumab in NMO.
2018 – present	Lauren Totonis, Master's in Nursing at Johns Hopkins University, mentoring for Research Honors Program with NMOSD project involving symptom co-occurrence and effect on quality of life.

CLINICAL ACTIVITIES

Certification

1999 – present	Nursing License, State of Maryland, license #: R145581
2003 – 2009	Certified Neurologic Registered Nurse (CNRN)
2009 – present	Multiple Sclerosis Nurses International Certification (MSCN)
2014 – present	Rare Neuroimmunologic Disorders Certification (CRND)

Community Service

July 2007	Medical Advisor, *Transverse Myelitis Association Family Camp,* Victory Junction Gang Camp (Randleman, NC)
July 2013	Medical Advisor, *Transverse Myelitis Association Family Camp,* the Center for Courageous Kids (Scottsville, KY)
August 2014	Medical Advisor, *Johns Hopkins Transverse Myelitis Center Adventure Camp,* Adaptive Sports Center (Crested Butte, CO)

ORGANIZATIONAL ACTIVITIES

Editorial Activities

Journal Peer Review activities:

Annals of Neurology, 2015

JAMA Neurology, 2017

Journal of the Neurological Sciences, 2017 – 2018

Multiple Sclerosis and Related Disorders, 2018

International Journal of Multiple Sclerosis Care, 2018 – 2019

Elected and Appointed Board and Committees Memberships

2014 – present	Inaugural Board Member, *Certified Rare Neuroimmunologic Diseases,* Consortium of Multiple Sclerosis Centers
2016 – present	Focus Group Member, *Continuing Professional Education Committee,* Consortium of Multiple Sclerosis Centers
2016 – present	Research Committee Member, International Organization of Multiple Sclerosis Nurses
2017 – present	Board of Directors, International Organization of Multiple Sclerosis Nurses
2018 – present	NMO International Clinical Consortium Member, Guthy Jackson Charitable Foundation
2018 – present	Research Committee Co-Chair, International Organization of Multiple Sclerosis Nurses

Professional Societies

1994 – 1996	Order of Omega Leadership Fraternity
1999 – present	Sigma Theta Tau International Honor Society of Nursing
2007 – present	International Organization of Multiple Sclerosis Nurses

2008 – present	Consortium of Multiple Sclerosis Centers
2010 – present	American Academy of Neurology

Conference Organizer/Session Chair

June 2013	Johns Hopkins Transverse Myelitis Center Patient Symposium, Organizer
June 2014	Johns Hopkins Transverse Myelitis Center Patient Symposium, Organizer
October 2014	Johns Hopkins Neuromyelitis Optica Patient Day, Organizer
June 2015	Johns Hopkins Transverse Myelitis Center Patient Symposium, Organizer
August 2015	Johns Hopkins Neuromyelitis Optica Patient Day, Organizer

RECOGNITION

Awards

May 2010	Consortium of Multiple Sclerosis Centers Scholarship
May 2017	Sigma Theta Tau International Honor Society of Nursing Research Award
September 2017	TL1 Trainee Award through the Johns Hopkins Institute for Clinical and Translational Research Predoctoral Clinical Research Training Program (PCRTP), funded by the National Institutes of Health
April 2018	Burroughs Wellcome Fund Trainee Award on behalf of the Translational Science 2018 Program Committee
April 2018	TL1 Blue Ribbon Poster Award at Translational Science 2018 Annual Meeting

Invited Talks

September 2010	Invited Speaker, *Rare Neuroimmunologic Disorder Symposium,* University of Texas Southwestern Medical Center (Dallas, TX)
February 2011	Journal Club Facilitator, *"Freedom From Disease Activity in Multiple Sclerosis",* Multiple Sclerosis Association of America (New Orleans, LA)
April 2011	Invited Speaker, *Multiple Sclerosis 101,* Multiple Sclerosis Association of America (Springfield, MO)
November 2011	Expert Panel Participant, *Annual Conference and Bernice Schacter Research Symposium,* National Multiple Sclerosis Society, Delaware Chapter (Newark, DE)
November 2013	Invited Speaker, *Updates on Neuromyelitis Optica,* International Organization of Multiple Sclerosis Nurses (online webinar)
October 2014	Invited Speaker, *Neuromyelitis Optica: Symptom Management,* Johns Hopkins Neuromyelitis Optica Patient Day (Baltimore, MD)

May 2015	Invited Speaker, *Neuromyelitis Optica: Diagnosis and Treatment,* Consortium of Multiple Sclerosis Centers Annual Meeting (Indianapolis, IN)
August 2015	Invited Speaker, *Pain in NMO,* Johns Hopkins Neuromyelitis Optica Patient Day (Baltimore, MD)
June 2016	Invited Speaker, *Neuromyelitis Optica Spectrum Disorder: Diagnosis, Epidemiology and Management,* Consortium of Multiple Sclerosis Centers Annual Meeting (National Harbor, MD)
June 2016	Invited Speaker, *How to Navigate the Healthcare Team*, Johns Hopkins Transverse Myelitis Center Patient Symposium (Baltimore, MD)
December 2016	Invited Speaker, *Pain in Neuromyelitis Optica Spectrum Disorder,* Harvard Medical School Neuromyelitis Optica Patient Day (Boston, MA)
May 2017	Invited Speaker, *Neuromyelitis Optica Spectrum Disorder: Diagnosis, Epidemiology and Management*, Consortium of Multiple Sclerosis Centers Annual Meeting (New Orleans, LA)
October 2017	Invited Speaker, *Neuromyelitis Optica Spectrum Disorder and Optic Neuritis,* Transverse Myelitis Association Rare Neuro-Immune Disorders Symposium (Columbus, OH)
October 2017	Invited Speaker, *Recognizing and Treating Neuropathic Pain,* Transverse Myelitis Association Rare Neuro-Immune Disorders Symposium (Columbus, OH)
October 2017	Invited Panelist, *Neuropathic Pain,* Transverse Myelitis Association Rare Neuro-Immune Disorders Symposium (Columbus, OH)
October 2017	Invited Speaker, *Are New Drugs on the Horizon for NMOSD?,* Transverse Myelitis Association Rare Neuro-Immune Disorders Symposium (Columbus, OH)
March 2018	Invited Panelist, *Ask the Expert*, Guthy Jackson Charitable Foundation Neuromyelitis Optica Patient Day (Los Angeles, CA)
April 2018	Invited Speaker, *Improving NMO Patient Quality of Life,* Guthy Jackson Charitable Foundation Academic Neuromyelitis Optica Roundtable Meeting (Los Angeles, CA)